NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: GID-MT554 KardiaMobile for the ambulatory detection of atrial fibrillation

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Document cover sheet

Assessment report: GID-MT554 KardiaMobile

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EAC sign-off: Andrew Sims

Version number	Brief description of changes	Author/reviewer (e.g. J Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
0.1	Start report	K Keltie	30/03/2021	
0.2	Completing sections	K Keltie	01/04/2021	
0.3	Review of technical section	D Bousfield,	13/04/2021	
0.4	Added sections, QA of study characteristics tables, review	K Keltie, G Fairlamb, J Burn, M Drinnan	14/04/2021	
0.5	Summary of evidence, QA of critical appraisal tables	K Keltie, R O'Leary	20/04/2021	
0.6	Review of clinical narrative	R O'Leary	22/04/2021	
0.7	QA of remaining study characteristics tables, addition of adverse events, summaries, review of clinical evidence section	K Keltie, G Fairlamb, R O'Leary	23/04/2021	
0.8	Formatting, adding summary	K Keltie	26/04/2021	
0.9	Reviewing against editorial style guide	G Fairlamb	27/04/2021	

0.10	Adding executive summary, formatting	K Keltie, E Belilios	27/04/2021	
0.11	Review	A J Sims	30/04/2021	
0.12	Responding to reviewer comments, starting economic write up	K Keltie	30/04/2021	
0.13	QA of economic table, QA of economic critical appraisal, additional write up of economics	R O'Leary [QA], K Keltie	04/05/2021	
0.14	Review of economics	R O'Leary	05/05/2021	
0.15	Continue economics narrative	K Keltie,	06/05/2021	
	Literature search write up added	A Inskip, F Beyer	10/05/2021	
0.16	Review of economics	A J Sims	12/05/2021	
0.17	Addressing comments	K Keltie	12/05/2021	
0.18	Additional write up of economics	K Keltie	13/05/2021	
1.0	Clean version for NICE	K Keltie	13/05/2021	13/05/2021
1.1	Including responses from company	K Keltie	17/05/2021	
1.2	Addressing comments from NICE, QA of economic model critical appraisal checklist, additional narrative on published economic studies	K Keltie, R O'Leary	18/05/2021	
1.3	Checking NICE, expert, and company comments have been addressed	R O'Leary	20/05/2021	
1.4	Additional write up of economics, formatting. Additional QA.	K Keltie, R O'Leary	21/05/2021	
1.5	Review	A J Sims	24/05/2021	

1.6	Addressing comments from review	K Keltie	25/05/2021	
1.7	Pre-submission checks	E Belilios	25/05/2021	
1.8	Adding conclusions and executive summary	K Keltie	25/05/2021	
1.9	Final review and sign-off	A J Sims	26/05/2021	
1.10	Final QA	K Keltie	26/05/2021	
2.0	Clean version for NICE	K Keltie	26/05/2021	27/05/2021
2.1	Changes following company fact check	K Keltie, A J Sims	02/06/2021	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT551 KardiaMobile for the ambulatory detection of atrial fibrillation

External Assessment Centre report

Produced by: Newcastle External Assessment Centre

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Date completed: **27/05/2021**

Contains confidential information: yes

Number of attached appendices: 6

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

None.

Acknowledgements

Adrian Brodison, Consultant Cardiologist, University Hospitals of Morecambe Bay NHS Foundation Trust.

Ruth Chambers, Ex-Staffordshire clinical lead for technology enabled care services programme, digital workstream and Honorary Professor Keele University, Visiting Professor Staffordshire University.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
A&E	Accident and Emergency
AF	Atrial fibrillation
AFEQT	Atrial fibrillation effect on quality of life
CER	Cardiac event recorder
CHEERS	Consolidated health economic evaluation reporting standards
CI	Confidence interval
DSA	Deterministic sensitivity analysis
EAC	External Assessment Centre
ECG	Electrocardiogram
ESC	European Society of Cardiology
ELR	External loop recorder
GDPR	General data protection regulation
GI	Gastrointestinal
HADS	Hospital anxiety and depression scale
HRQoL	Health-related quality of life
ICERs	Incremental cost-effectiveness ratios
ICH	Intracerebral haemorrhage
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE DG	NICE diagnostic guidance
NOAC	Novel oral anticoagulants
PRESS	Peer review of electronic search strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
QA	Quality assurance
QALYs	Quality adjusted life years
QUADAS	Quality assessment of diagnostic accuracy studies
RCT	Randomised controlled trial
RR	Relative risk
SF-36	Short form health survey
SPARC	Stroke prevention in atrial fibrillation risk tool
STROBE	Strengthening the reporting of observational studies in epidemiology
TIA	Transient ischaemic attack
YHEC	York Health Economics Consortium

Executive summary

In this assessment report, “company” refers to AliveCor Inc., who were represented in the clinical and economic submissions by Device Access UK and Optimax Access UK respectively. “EAC” refers to the Newcastle External Assessment Centre, the authors of this assessment report. “Clinical experts” refers to individuals, approved by NICE, who advised the EAC in the preparation of this report.

KardiaMobile consists of the KardiaMobile Heart Monitor portable electrocardiogram (ECG), available as a single or 6-lead device, and the Kardia app which works with a compatible mobile device (such as a smartphone or tablet) to analyse the ECG recording. The claimed benefits surround the portable nature of the device and its ease of use, leading to earlier detection of atrial fibrillation (AF) and subsequent improved patient outcomes.

The company identified a total of 33 studies from their literature search. The EAC considered 15 of these as out of scope and identified an additional 14 papers from an independent search. A total of 32 studies were included in the clinical evidence review: 7 RCTs, 7 diagnostic accuracy studies, 1 case-control, 16 single-arm observational studies, and 1 case report; 14 were abstracts only. Some studies reported on different outcomes from the same population. In the combined evidence KardiaMobile was used in 2,801 unique patients. None of the included studies reported on the use of KardiaMobile-6L. The studies were heterogeneous in nature and differed in: population, AF prevalence, setting, usage (frequency and duration of KardiaMobile recordings) and reference/comparator. Four studies compared the automated rhythm classification of Kardia Mobile with clinical interpretation: sensitivity of AF detection ranged from 92 to 99%, specificity ranged from 92 to 98%. Six comparative studies reported that KardiaMobile detected AF more frequently than ‘standard care’; however standard of care varied across studies. Two RCTs confirm that KardiaMobile reduced the time to AF detection. Nine studies reported on its ease of use. Two RCTs have demonstrated improvements in Atrial Fibrillation Effect on Quality-of-Life (AFEQT).

The company identified 5 published economic studies. The EAC considered 2 of these as out of scope, however the remaining three studies (two set in the UK) demonstrated KardiaMobile to be cost saving, largely through the reduction in healthcare appointments (emergency care, GP, ECG referral). The company provided a *de novo* Markov model (described across 20 worksheets, including more than 150 parameters) written in Microsoft Excel, consisting of two phases: diagnosis (maximum 100 days) and management (5 years). Two updates of the model were received. The company base-case scenario reported that the per-patient pathway costs over 5 years associated with using KardiaMobile were £2941, and was cost-saving by £322, £320, £333 and £383 per person over 5 years when compared to 24 hour, 48 hour, 7 day Holter, and 14 day Zio patch monitoring respectively. The EAC considered the model as overly complex, not transparent and not verifiable. The EAC did not agree with underlying structural assumptions, parameter choice or their implementation in the *de novo* model. With a simple cost-calculator informed by 6 comparative studies from the clinical evidence, the EAC estimated the cost consequences of reduced strokes associated with increased AF detection with KardiaMobile The EAC found KardiaMobile to be cost-saving using results from 3 out of 6 comparative studies; saving between £144 and £490 per patient when compared withHolter or external loop recorders driven by increased detection of AF with KardiaMobile and the predicted number of strokes avoided at 1 year.

The EAC is satisfied that the clinical evidence supports KardiaMobile being made available as an option in the diagnosis or monitoring of AF. Adverse events are unlikely, however clinical interpretation of all recorded ECGs is required, in line with the device instructions for use, to limit the impact of false negative and false positive results. Large variation in NHS practice and heterogeneity in patients likely to benefit from KardiaMobile limits the value of further research. The EAC considers it plausible for KardiaMobile to be cost-saving. However, additional modelling including probabilistic sensitivity analysis is warranted to estimate the magnitude of the cost saving and its confidence interval, in various scenarios, if KardiaMobile is implemented in the NHS.

1 Decision problem

The company did not propose any variation to the decision problem specified in the final scope (NICE, 2021), but acknowledged that they could not provide evidence on all of the outcomes due to lack of evidence, Table 1.

Table 1: Scope of the decision problem

Decision problem	Scope	Proposed variation in company submission
Population	Adults (18 years or older) with known or suspected atrial fibrillation are referred for ambulatory ECG monitoring by a clinician in primary, secondary, or tertiary care.	No variation
Intervention	The KardiaMobile system: KardiaMobile hardware (single-lead or 6-lead ECG monitor) and KardiaMobile app.	No variation
Comparator(s)	Current pathway for atrial fibrillation detection, which includes ECG (a 12-lead ECG, performed and interpreted by a trained healthcare professional, is the reference standard for assessing diagnostic accuracy) and ambulatory monitoring (Holter or event monitoring).	No variation
Outcomes	System outcomes • Diagnostic yield and accuracy (sensitivity and specificity) • Atrial fibrillation burden, including the number of symptomatic and asymptomatic atrial fibrillation events detected during the recording period, and the time spent in atrial fibrillation • Time to detect first or recurrent atrial fibrillation events • Time to diagnosis or rule out of atrial fibrillation • Time to initiation of treatment (control symptoms or preventing the risk of future events) • Rate of test failure • Data transfer failure • Rate of fail to classify • Rate of secondary care referral • Total number of hospital outpatient appointments for investigation • Hospital admission	Only outcomes that were reported in the included clinical studies were included.

	• Number of outpatient visits and staff time for undertaking and analysing diagnostic tests • Number of visits to GP or urgent care • Number of further tests needed in addition to KardiaMobile • Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment) • Mortality Patient outcomes: • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction Health-related quality of life Device-related adverse events	
Subgroups to be considered	Adults referred for ambulatory ECG monitoring, who are symptomatic or asymptomatic. Adults referred for ambulatory ECG monitoring in primary care. Adults referred for ambulatory ECG monitoring in secondary care.	No variation
Special considerations, including issues related to equality	KardiaMobile is not approved for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators, or other implanted electronic devices. The device may not be suitable for people who cannot remain still or have problems holding the device; for example, people with tremor may have difficulty recording an accurate trace. People are not able to use the device if they do not have a compatible smart device to access the KardiaMobile app. Age and disability are protected characteristics under the Equality Act. Full details of contraindications are listed in the instructions for use for KardiaMobile.	No variation

The EAC has made the following clarifications on other aspects of the scope.

1.1. Population

The population described in the scope is “Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care” (NICE, 2021). This excludes use of the device for single-time point Lead-I ECG testing, and asymptomatic screening. There is already existing guidance in lead-I ECG devices using single-time point testing in primary care (NICE DG35, 2019).

1.2. Intervention

The company previously marketed the KardiaBand device; a smart band designed for use with an Apple smart watch. However, given the different mode of use (wearable) and that KardiaBand was removed from sale in 2019, the EAC has excluded evidence that includes KardiaBand as the intervention.

2 Overview of the technology

The KardiaMobile Heart Monitor (previously named the AliveCor Heart Monitor, AliveCor Inc.) is a class IIa portable electrocardiogram (ECG) recorder with valid certification provided by a notified body until 2023. The monitor works with a compatible smartphone or tablet computer running the Kardia app, which analyses the ECG recording.

KardiaMobile is available as a single-lead (KardiaMobile-1L) or 6-lead (KardiaMobile-6L) device. KardiaMobile-1L has two electrode pads on the top surface; two fingers from the left hand are placed onto one electrode and two fingers from the right hand are placed onto the other electrode. KardiaMobile-6L has three electrodes; two electrode pads on the top surface (same use as KardiaMobile-1L) and an additional electrode pad on the bottom surface which is placed on the left leg (intended to contact the knee or ankle). The patient must keep still and maintain skin contact with the electrodes whilst a recording is being taken (sample rate of 300 Hz, 16-bit samples); the default recording duration is 30 seconds but can be extended to 5 minutes. The company recommends that recordings are taken with the patient sitting (or keeping as still as possible to reduce muscle noise) daily, or whenever

arrhythmia symptoms are experienced. There is no restriction on the number of times the device could be used. A patient may also be given specific advice by their physician on how often to use the device and in-app reminders can be set.

The KardiaMobile Heart Monitor must be used in conjunction with a standard internet-enabled mobile phone or tablet with the Kardia app installed. The KardiaMobile Heart Monitor sends the recording wirelessly (KardiaMobile-1L uses high frequency sound waves – which the EAC considers may be influenced by noise; KardiaMobile-6L uses Bluetooth) to the mobile device, where it can be viewed in the Kardia app. The app saves and analyses data from the monitor, and works on devices running Apple or Android operating systems (a list of compatible devices is available on the company's website). The ECG signal is smoothed using a high-order filter on the QRS segment, a low-order filter on the non-QRS segment and threshold fit smoothing on the low-amplitude high frequency noise (AliveCor Inc, 2017). The output of the Kardia app includes the smoothed ECG trace, filter information, name, heart rate, date of birth, time and date stamp and classification of the rhythm to one of the following categories:

- normal (sinus rhythm)
- possible AF,
- bradycardia,
- tachycardia
- unreadable (ECG not interpreted, possible interference).
- unclassified (not normal, possible AF, bradycardia or tachycardia, and interference not detected)

When the outcome is displayed to the patient, they are informed that KardiaMobile does not check for heart attacks. The app also instructs if the patient is symptomatic or has any concerns they should contact a medical professional.

The company has confirmed that bradycardia and tachycardia categories were introduced in a software update in April 2019; however these are out of scope for this guidance which focused on atrial fibrillation only. The company has confirmed that additional classifications (Premature Ventricular Contractions, Sinus rhythm with supraventricular ectopy, and Sinus rhythm with wide QRS) are available using premium KardiaCare membership from April 2021 (not included within the company submission)(EAC communications log, 2021). The company confirmed that the automated classification only uses lead-I of KardiaMobile-1L and KardiaMobile-6L (EAC communications log, 2021).

An internet connection is required to download the Kardia app. Personal data (name, date of birth, sex, height, email and password) is required from the patient when setting up an account on the Kardia app. Medical history (angina, AF, cardiomyopathy, coronary heart disease, diabetes, heart failure, heart murmur, high blood pressure, high cholesterol, long QT, myocardial infarction (MI), palpitations, other cardiac disease, other arrhythmia, smoking), weight and blood pressure measurements are optional, but not required. The patient does not require internet access to record the ECG trace and obtain an automatic ECG classification. Note that the patient can optionally add additional information to each recorded ECG trace. The company has stated that after the ECG trace is closed by the patient, and when the device has a Wi-Fi or mobile connection, the recording automatically synchronises with a secure encrypted GDPR-compliant cloud server (EAC communications log, 2021). The company report that upload of medical data to the cloud server or local storage of the ECG and notes can be turned off by the patient via a setting within the Kardia app (however this does not stop upload of personal data) (EAC Correspondence Log, 2021). The AliveCor Privacy Policy specifies how data are used and shared.

The freely-downloadable Kardia app includes: unlimited ECG readings, storage of ECGs and ability to share them by email, as well as tracking of manually entered weight and blood pressure. The KardiaMobile instructions

for use state that readings taken by the monitor should be reviewed by a medical professional for clinical decision making.

The premium KardiaCare membership (available for a fee payable by the patient) offers additional services: ECG review by a private professional every 90 days, monthly heart health report, automatic ECG sharing with family or caregivers, medication tracking, cloud storage and security to allow recordings to be accessed on any device. The KardiaPro platform is an optional extra for healthcare professionals which allows remote monitoring of Kardia app patients and generation of reports (the cost of KardiaPro software is based on the number of connections needed per institution). The KardiaStation app is an optional extra designed to take ECG recordings of patients within a healthcare setting, the results from which are uploaded to the KardiaPro platform. KardiaCare, KardiaPro and KardiaStation are not included within this assessment report.

The KardiaMobile-1L Heart Monitor and Kardia app were CE-marked as a Class IIa medical device in 2015. KardiaMobile-6L Heart Monitor was CE marked as Class IIa medical device in 2019. The combination of the KardiaMobile Heart Monitor (1L or 6L) with Kardia app are described collectively as KardiaMobile for the remainder of this report.

KardiaMobile is not intended for use in children (under 18 years of age) and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices.

The EAC considers the potentially innovative aspect of this technology is that it can be used in people with suspected paroxysmal AF without the need to refer for a 24-hour ambulatory ECG assessment or event recording. Because the KardiaMobile Heart Monitor is portable, readings can be taken at home, or in any other setting, and at any time of the day. This may increase the diagnostic yield of an arrhythmic episode being detected and recorded.

3 Clinical context

The NICE guideline on the diagnosis and management of atrial fibrillation: recommends manual pulse palpation for people with suspected AF to detect an irregular pulse (NICE NG196, 2021). If an irregular pulse is detected, a 12-lead ECG should be performed whether or not the patient has symptoms. For patients with suspected paroxysmal atrial fibrillation undetected by 12-lead ECG recording:

- Use a 24-hour ambulatory ECG monitor if asymptomatic episodes are suspected or symptomatic episodes are less than 24 hour apart.
- Use an ambulatory ECG monitor, event recorder or other ECG technology for a period appropriate to detect atrial fibrillation if symptomatic episodes are more than 24 hours apart.

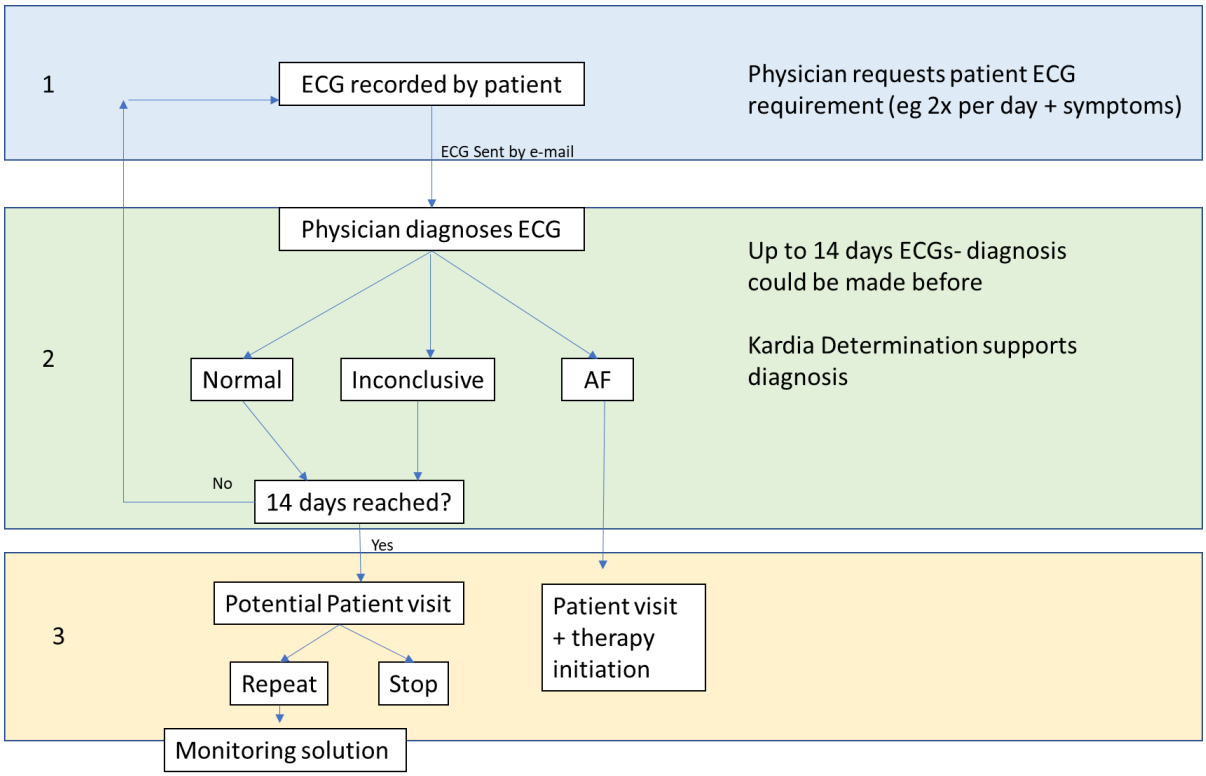
The 2020 European Society of Cardiology guidelines for the diagnosis and management of AF state that a 12-lead ECG or a single-lead ECG trace of 30 seconds or more are required to diagnose AF.

Within Section 3 of the Clinical Submission, the company proposes that KardiaMobile replaces external event recorders and may be used alongside continuous ambulatory (for example, Holter) monitoring in adult symptomatic patients. The company provided an additional diagram to describe how the work flow of KardiaMobile when used in an NHS setting (13/05/2021, EAC Communications Log, 2021), Figure 1.

The company confirmed that the prescribing clinician would advise patients on the frequency and duration of KardiaMobile monitoring. Four of the five clinical experts approached had previous experience with KardiaMobile (EAC Communication Log, 2021), and stated variable frequency of use dependent upon population; for example patients with palpitations may be told to record ECG when symptomatic, whereas post-stroke patients may be advised to record an ECG up to 4 times a day. The clinical experts also stated varied duration of use dependent upon population between 14 and 90 days. The company also confirmed that the clinician would advise the patient which

results were to be emailed for clinical review. The clinical experts stated variation in practice; two reported reviewing all recordings, two reviewed only symptomatic recordings.

Figure 1: Work flow of KardiaMobile in NHS setting.



Note that clinical review of ECGs is a requirement due to the device instructions for use stating that the output of Kardia app cannot be used as a clinical diagnosis. The EAC considers that the proposed work flow (described in Figure 1) is dependent upon the patient emailing the ECG recording. This proposed process could introduce bias through missing data (for example patient may forget to send email), and the security of the approach should be considered (as the ECG trace contains patient identifiers and is emailed from the patients personal email as an attachment).

The EAC reviewed the AliveCor Privacy Policy against the six principles of the NHS Data Protection Policy. The EAC considered that healthcare providers prescribing KardiaMobile may find it difficult to comply with the NHS Data Protection Policy. The EAC therefore recommends that AliveCor consider the following:

- data minimisation within the Kardia app,
- expanding the Privacy Policy statement to include explicit description of different aspects of consent (including how users can opt-in and opt-out),
- removal of premium service marketing when the device is used in an NHS setting.

Special considerations, including issues related to equality

Some people with disabilities or with conditions affecting manual dexterity or hand tremors may not be able to record an electrocardiogram on the KardiaMobile device (which requires skin contact for 30 seconds or more) or use the Kardia app. Patients require access to an internet-enabled mobile phone or tablet, and must have an email address to create an account. The proportion of patients without access to this technology may be higher in some groups, for example older people (who are the greatest risk of AF) or those with lower income. The KardiaMobile is not intended for use in children and is contraindicated in people with implantable electronic devices (including pacemakers and implantable cardioverter defibrillator). Disability, age and sex are protected characteristics under the Equality Act (2010).

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company search strategy was peer reviewed using the PRESS tool (McGowan *et al.* 2016), Appendix A1. The structure combined two main concepts (atrial fibrillation and the product) and each concept was covered by a range of alternative terms, which was considered appropriate. The search strategy was considered generally fit for purpose, however several elements of the company literature search could have been improved. Candidate terms were used in Embase without equivalent keyword searches. Furthermore, the candidate terms were exploded which, since candidate terms are not part of the Emtree subject heading hierarchy, means they may not have contributed to the search at all. Some of the non-product-specific alternative keyword

terms were quite broad and not qualified further (for example ‘mobile monitoring’). Conversely, some were too specific (for example ‘single lead ecg’ which would not cover ‘single lead electrocardiogram’). Some terms were considered redundant adding complexity to the search without being more comprehensive (for example ‘portable single lead ecg’, ‘single lead ecg recorder’, ‘portable single lead ecg recorder’ were all already covered by ‘single lead ecg’).

The EAC conducted an updated search (described in Appendix A2). This updated search used the same general structure, removed redundant terms, applied changes to product-specific terms and introduced several search elements to find a pragmatic quantity of additional results with the greatest chance of relevancy based on non-product-specific terms (results that did not mention Kardia or AliveCor by name in the database record, but which might in the full article). These search elements utilised proximity (for example a smartphone term *near* an ECG term) or a combination of multiple requirements (for example a smartphone or ehealth term AND a single or six lead term AND an ECG term).

The searches were run by the EAC on 12th April 2021 on Medline (Ovid), Embase (Ovid), CINAHL (EBSCOhost), CENTRAL and CDSR (Cochrane Library), Clinicaltrials.gov, EU Clinical Trials Register and IDEAS/RePEc. The WHO ICTRP search portal was not available at the time of searching. A total of 690 results were initially retrieved, of which, 451 remained after deduplication. The titles and abstracts of each were sifted according to the final published scope (NICE 2021) by a single reviewer. At this stage, sensitivity was maximised to minimise exclusion of relevant papers. Full papers were retrieved and reviewed by a single reviewer. The study selection process is illustrated as a PRISMA diagram in Appendix A3.

4.2 *Included and excluded studies*

The company identified a total of 24 peer-reviewed studies and 9 conference abstracts they considered were relevant and within the scope of the decision problem.

The EAC excluded 15 of the studies included by the company due to incorrect population (device used in screening or single-time point testing), intervention (KardiaBand), and outcomes (AF detection not reported), Table 2.

The EAC identified two more recent studies which supersede those submitted by the company: an RCT by Guhl *et al.* 2020 (which supersedes the Magnani *et al*. 2017 pilot study), and RCT by Koh *et al.* 2021 (published on 30 March 2021; one day after the company Clinical Submission, which supersedes the Koh *et al.* 2019 conference abstract). The EAC identified an additional four peer-reviewed studies and ten conference abstracts not included in the company submission.

Table 2: Studies included by company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Treskes *et al*. 2020 Netherlands [TheBox study; NCT02976376]	RCT (single-centre) Intervention (n=100): 2 visits to outpatient clinic at 3 and 12 months, 2 video appointments at 1 and 6 months. Patients instructed to use 4 smartphone compatible devices daily: BP monitor, step counter, weight scale and KardiaMobile-1L (ECG interpreted by healthcare professional). ☒☑ Control (n=100): standard care (defined as 4 visits to outpatient clinic at 1, 3, 6 and 12 months after AMI with 12-lead ECG and BP measurement. 24-hour Holter monitor also taken at 3 and 6 months. TTE performed at 6 and 12 months) ☑	Patients aged 18 years and older admitted to cardiology department with AMI. ☑ Setting: cardiology department	Controlled BP after one year, patient satisfaction, patient adherence, mortality, hospitalisations☒☑	Excluded based on outcome (BP control); did not address decision problem.

Halcox *et al.* 2017 UK [REHEARSE-AF study; ISRCTN10709813.]	RCT Intervention (n=500): KardiaMobile-1L (participants instructed to take twice weekly recordings; Monday and Wednesday recommended plus additional submissions if symptomatic) interpreted by automated software and physiologist-led ECG reading service (abnormal ECGs reviewed by cardiologist) ☑ Control (n=501): standard care (follow-up by GP) ☑ [All patients contacted by study team at 12, 32 and 52 weeks. Clinical event confirmed by clinical chart review]	Participants aged 65 years or more, with CHA_2DS_2-VASc score of 2 or above, not in receipt of OAC therapy, without a known diagnosis of AF currently, a known contraindication to anticoagulation, or permanent cardiac pacing implantation. Participants were required to have access to the internet via Wi-Fi. ☒☑ Setting: Participants recruited from local GP surgeries or recruited when attending the research unit for other reasons	New AF diagnoses, patient compliance, adverse events, patient satisfaction, quality of life, health resource usage☑	Excluded based on screening (population asymptomatic and therefore would not routinely be referred for ECG); did not address decision problem.
Bhavnani *et al.* 2018 India	RCT (multi-centre); randomisation via SPSS	Outpatients (adults, paediatric and pregnant patients) with new or established diagnosis of	Time to treatment with valvuloplasty or valve replacement, atrial arrhythmia,	Excluded based on mixed intervention, primary outcome was not relevant to decision problem (time to valvuloplasty), outcome

[ASEF-VALUES, NCT02881398]	Intervention (n=139 analysed): mHealth (pocket ECG (VScan), smartphone-connected oximetry and blood pressure monitor, tri-axial activity monitor, KardiaMobile-1L, PoC fingerstick B-type natriuretic peptide). ☒☑ Control (n=114 analysed): Standard care☑	structural heart disease (included valvular disease, left or right ventricular failure and congenital heart defects). ☒☑ Setting: outpatients	cardiovascular hospitalisation, death ☒☑	includes atrial arrhythmia (atrial fibrillation or atrial flutter, supraventricular tachycardia, or ventricular arrhythmias); did not address decision problem.
Haberman *et al.* 2015 US	Diagnostic accuracy (n=381, of which 130 from cardiology clinic) Reference test: 12-lead ECG (interpreted by electrophysiologists) ☑ Index test: KardiaMobile-1L (interpreted by electrophysiologists) ☑	Participants included University of Southern California Division 1 Athletes, asymptomatic students and 130 ambulatory cardiology clinic patients. ☒☑ Setting: ambulatory cardiology clinic	Correlation between automated algorithm interpretation of smartphone and 12-lead ECG, diagnostic accuracy, patient satisfaction ☒☑	Excluded based on single time point testing (overlap with NICE DG35).
Karregat *et al.* 2021 Netherlands	Diagnostic accuracy (online study using 80 case vignettes)	GPs contacted via email, only those responding included in study. 80 KardiaMobile-1L traces from a preview study were	Diagnostic accuracy of GP interpretation (with and without automated software output). ☑	Excluded based on study design (sampled online vignettes) and single time point testing (overlap with NICE DG35) and outcome

	Reference test: KardiaMobile with classification of ECG by two independent cardiologists, a third as referee ☑ Index test: KardiaMobile with classification of the ECG by GP or KardiaMobile algorithm☑	used (Himmelreich *et al.* 2019) which were obtained from consecutive primary care patients who were assigned to 12-lead ECG for any non-acute indication as ordered by local GP. ☒		(diagnostic accuracy of GPs).
Wasserlauf *et al.* 2019 US	Diagnostic accuracy Intervention: Apple watch with KardiaBand ☒	Two datasets: 1) anonymous training dataset of continuous heart rate, activity an ECG data acquired from 7500 AliveCor users to train the AF-sensing watch, 2) validation cohort of 26 patients with previously implanted cardiac monitor and history of AF. ☒ Setting: ambulatory	Diagnostic accuracy☑	Excluded based on intervention (KardiaBand no longer available) and population (KardiaMobile contraindicated in patients with implantable cardiac device).
Tarakji *et al.* 2015 US	Diagnostic accuracy (single-centre) (n=55)	Patients aged 18 to 75 years old, undergoing AF ablation with or without	Diagnostic accuracy, quality of ECG, patient satisfaction (ease of use availability). ☑	Exclude based on comparator (not

	Reference test: transtelephonic monitor (Pacetrack, Mednet Healthcare Technologies Carry All EZ Monitor, Instromedix) ☒ Index test: KardiaMobile-1L. ECG tracing categorised as sinus, AF or not interpretable by blinded electrophysiologist ☑ [Patients asked to record both simultaneously when symptomatic or at least once a week]	atrial flutter ablation who had an iPhone 4, 4s, 5. ☑ Setting: tertiary centre		representative of current NHS care).
Rajakariar *et al.* 2018 Australia	Diagnostic accuracy (multi-centre) (n=50) Reference test: Each patient had 12-lead ECG reviewed by a blinded cardiologist. ☑ Index test: Each patient had KardiaMobile-1L ECG. In patients where 12-lead ECG confirmed	Consecutive patients 18 years or older on continuous cardiac monitoring (5-lead, Philips IntelliVue) ☑ Setting: tertiary university hospitals	Diagnostic accuracy (Clinician diagnosis based on KardiaMobile ECG trace, Clinician diagnosis of 12-lead ECG, KardiaMobile diagnosis). ☑	Excluded based on single time point testing (overlap with NICE DG35)

	atrial flutter a modified position of KardiaMobile taken (one hand and one leg). All KardiaMobile traces reviewed by two blinded cardiac electrophysiologists. ☒☑			
Selder *et al.* 2020 Belgium	Cohort (n=60) Intervention: Wavelet (PPG wristband) on one arm, and Apple watch with KardiaBand on other arm. ☒	Guests and employees of senior care organisation aged 18 years or older, without pacemaker. ☒ Setting: Community senior care organisation	Recording quality, unclassified, diagnostic performance☑	Excluded based on intervention (KardiaBand no longer available) and population (would not be referred for ECG). Comparator also out of scope (PPG).
Soni *et al.* 2019 India [SMARTIndia]	Cohort (n=2074) Intervention: KardiaMobile-1L (recording taken three times over a five day period) interpreted by automated software and cardiologist ☑	Adults 40 years or more living in rural region☒ Setting: community	AF detection, unclassified rhythms. ☑	Excluded based on screening population (would not be referred for ECG)
Soni *et al.* 2016 India	Cohort (n=235) Intervention: KardiaMobile-1L and pulse data (recorded serially for two minutes each on five consecutive days for six weeks)	Adults 50 years or more living in rural region☒ Setting: community	Device malfunction, AF detection, unclassified rhythms. ☑	Excluded based on screening population (would not be referred for ECG)

	interpreted by cardiologist ☑			
Grieten *et al.* 2017 Belgium	[Abstract] Cohort (n=1056) Intervention: KardiaMobile-1L and FibriCheck (if one indicated irregular rhythm then a 12-lead ECG was taken for verification) ☑	Not reported Setting: community screening☒	Diagnostic accuracy, AF detection, number of unreadable traces, recording quality. ☒	Excluded based on population (would not be referred for ECG, screening) and comparator (PPG).
Dankers *et al.* 2019	[Abstract] Diagnostic accuracy (n=60) Reference test: ECG traces interpreted by two independent blinded reviewers. Index test: KardiaBand and Wavelet (PPG wrist band) interpreted by software ☒	Participants older than 18 years, with no cardiac device. ☒ Setting: Mobile Health Unit	Diagnostic accuracy. ☑	Excluded based on intervention (KardiaBand no longer available) and population (would not be referred for ECG). Also single time point and comparator (PPG) out of scope.
Saxon *et al.* 2012 US	[Abstract] Cohort (n=54)	Attendees of a body computing conference who owned an iPhone. ☒ Setting: non-medical	Arrhythmia detection (not specific to AF), recording quality. ☑	Excluded based on population (would not be referred for ECG, screening) and usability

	Intervention: KardiaMobile-1L (range of 3 to 298 recordings taken during 8 week period) ☑			outcome (not exclusive to AF)
Bose *et al*. 2014 US	[Abstract] Cohort (n=8669) Intervention: KardiaMobile (A mean of 65 ECG recording per patient, average device-use duration of 158 days). ☑	Unselected group of US patients. Included patients enrolled in clinical trials of the device (15% of population) and those that were prescribed the device for self-monitoring. ☒ Setting: not reported	Patient use, AF detection. ☑	Excluded based on insufficient data on population (unlikely population would be referred routinely for ECG).
Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope. Abbreviations: AF atrial fibrillation; AMI acute myocardial infarction; BP blood pressure; ECG electrocardiogram; OAC oral anticoagulants; PoC point of care; PPG photoplethysmography; RCT randomised controlled trial; TTE transthoracic echocardiogram;				

A total of 32 remaining studies were considered by the EAC to be relevant (16 identified by the company, and 14 additional studies and 2 updates identified by the EAC). This included six broad populations, Table 3.

Table 3: Summary of evidence by population and study design

	Study design					
Population	RCT	Diagnostic accuracy	Case-control	Observational	Case report	Total
Undiagnosed palpitations	1	2	0	4	0	7 (including 3 abstracts); Table 4a
History of AF, who have received treatment (ablation, cardioversion, or medical therapy) to restore sinus rhythm and used KardiaMobile to identify recurrence	3	2	1	3	1	10 (including 4 abstracts); Table 4b
Patients with diagnosed AF to assess AF burden	2	2	0	3	0	7 (including 5 abstracts); Table 4c
Patients with transient AF after surgery or hospitalisation who reverted back to sinus rhythm prior to discharge, and used KardiaMobile to identify recurrence	0	0	0	2	0	2; Table 4d
Patients after stroke or TIA who were monitored using KardiaMobile	1	0	0	2	0	3 (including 1 abstract); Table 4e
Mixed population including patients with known or suspected AF	0	1	0	2	0	3 (including 1 abstract); Table 4f

Table 4a: Studies selected by the EAC as the evidence base: population included patients with undiagnosed palpitations

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Reed *et al.* 2019 UK [IPED study; NCT02783898]	RCT (multi-centre); permuted block randomisation by site. Intervention (n=124 available for analysis): ECG recorded and analysed using KardiaMobile and Standard care ☑ Control (n=116 available for analysis): Standard care (varied across centres) ☑ [Participants in both groups were admitted, referred or discharged by the treating clinician according to current local hospital protocols. Patients followed up to 90 days using electronic health records.]	Participants aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythm during these episode remains undiagnosed after emergency department assessment. ☒☑ Setting: Emergency departments and Acute medical units	Symptomatic rhythm detection (reported separately for atrial fibrillation), time to detection of symptomatic rhythm, time to detection of symptomatic cardiac arrhythmia (rhythm that is not sinus rhythm, sinus tachycardia or ectopic beats), emergency department presentations, mortality, hospital inpatient days, outpatient presentations, number of GP attendances, number of patients treated for cardiac arrhythmia, participant satisfaction and compliance, ease of use, cost-effectiveness, serious outcomes at 90 days. ☑	Contains patients aged less than 18 years.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Narasimha *et al.* 2018 US [NCT02005172]	Diagnostic accuracy (n=33) Reference test: external loop recorder pressed when symptoms felt. ECG traces reviewed by two blinded cardiologists ☑ Index test: KardiaMobile-1L activated at same time as external loop recorder. ECG traces reviewed by two blinded cardiologists ☑ [Monitoring period for both between 14 and 30 days; depending on insurance authorisation].	Patients 18 years or older presenting with palpitations to outpatient cardiology clinics with a non-diagnostic previous work-up (ECG and in some cases Holter monitor); symptoms occurring less often than daily, but more frequently than several times a month. ☑ Setting: outpatient cardiology clinic	Arrhythmia detection, diagnostic yield, patient compliance, patient symptom log diary, patient satisfaction (ease of use, portability). ☑	Software not used for diagnosis

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Dimarco *et al.* 2018 UK	Single-arm observational (n=148) Intervention: KardiaMobile (patients instructed to use when symptomatic) ☑	Patients referred to a cardiologist for investigation of palpitations occurring less than daily with a) access to a compatible smartphone and b) willingness and ability to use a device. Patients with a history of syncope were excluded. ☑ Setting: cardiology department	Detection of AF, time to diagnosis, unreadable. ☑	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Reed *et al.* 2021 UK	Single-arm observational (n=50) Intervention: KardiaMobile-1L ☑	Patients attending emergency department with palpitations or pre-syncope, with normal ECG who were subsequently referred, with compatible phone, tablet or watch. ☑ Setting: emergency department or acute medicine unit	Detection of symptomatic rhythm at 90 days ☑	Included watch (mixed intervention)
Onwordi *et al.* 2016 UK	[Abstract] Cohort (n=70) Intervention: KardiaMobile (used when symptomatic) ☑	Patients referred from primary care for investigation of palpitations or presyncope, with access to smart phone, symptoms less than weekly, no history of syncope. ☑ Setting: Hospital	AF detection, number of recordings ☑	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Goel *et al.* 2018 US	[Abstract] Diagnostic accuracy (multi-centre, n=50) Reference test: Holter monitor (24-hour) Index test: KardiaMobile (instructed to use when symptomatic over 30 days) ☑	Patients present to urgent care with palpitations ☑ Setting: urgent care	Detection of AF ☑	Sensitivity and specificity not reported (but concordant pairs reported).
Frey *et al.* 2020 France	[Abstract] Cohort (n=20) Intervention: KardiaMobile (patients instructed to take recordings when symptomatic, during one month follow-up) ☑	Patients with paroxysmal palpitations and negative 24-hour ECG ☑ Setting: cardiology department	Number of recordings, detection of AF, treatments. ☑	

Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope.

Abbreviations: AF atrial fibrillation; ECG electrocardiogram; RCT randomised controlled trial;

Table 4b: Studies selected by the EAC as the evidence base: population included patients with AF diagnosed post-treatment

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Goldenthal *et al.* 2019 US [iHEART study; NCT02731326 Additional outcomes reported from same population were included in the RCT by Caceres *et al.* 2020, and abstracts by Turchioe *et al.* 2019, Reading *et al.* 2018 and Reading *et al.* 2017]	RCT (single-centre); block randomisation age-matched ☑ Intervention (n=115): KardiaMobile used once per day plus when symptoms occurred. Patients also received motivational text messages three times per week relating to management of AF and risk factors. ☒☑ Comparator (n=123): standard care (not defined) ☑	Adults aged 18 years and over, undergoing catheter radiofrequency ablation or direct current cardioversion. All had history of documented AF and at least one AF risk factor (sedentary lifestyle, obesity, hypertension, smoking, diabetes). ☑ Setting: in cardiac electrophysiology clinic	Recurrence of AF or flutter (early: within first month after ablation, late: after one month), time to direct atrial arrhythmia, subsequent treatment, time to first treatment, all-cause hospitalisation, emergency room visits, frequency of KardiaMobile recordings, patient usage [Caceres *et al.* 2020: HRQoL, symptom severity, AF recurrence. Turchioe et al. 2019; number of recordings AF recurrence, ease of use. Reading *et al.* 2018 (n=50): AF recurrence, time to detection, symptoms. Reading *et al.* 2017 (n=50): Adherence rates and reasons for failing to transmit] ☒☑	Composite outcome (AF and flutter). Recurrence defined as KardiaMobile output or ECG in patients' electronic health record.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Hermans *et al.* 2021 Netherlands	Diagnostic accuracy (n=115) Reference test: Standard care for post-AF ablation outpatient clinic visits including Holter monitor (minimum 24 hours), at 3, 6 and 12 months. ☑ Index test: At one follow-up patients were provided with KardiaMobile-1L and instructed to use three times daily and when symptomatic (for four weeks duration). ☑ [Traces interpreted by two researchers (third as referee), and included automated software detection by Kardia app.]	Patients aged 18 years or older undergoing AF ablation, who had a smartphone and were able to operate KardiaMobile-1L. ☑ Setting: outpatient clinic	AF recurrence, patient satisfaction, ease of use, diagnostic accuracy, quality of KardiaMobile ECG trace, unclassified, unreadable. ☑	Holter monitor and KardiaMobile used at different time points across cohort.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
William *et al.* 2018 US	Diagnostic accuracy (single-centre) (n=52) Index test: 12-lead ECG interpreted by physician ☑ Reference test: KardiaMobile (automated algorithm detection, and physician interpreted) ☑ [KardiaMobile performed immediately after 12-lead ECG]	Patients with a diagnosis of AF who were admitted for anti-arrhythmic drug initiation (dofetilide or sotalol), 35 to 85 years of age, with history of paroxysmal or persistent AF, baseline corrected QT interval less than 470 ms or 500 ms if the QRS duration was greater than 120 ms. ☑ Setting: recordings were performed in patients admitted to hospital	Diagnostic accuracy, "unclassified" readings, ease of use, patient satisfaction. ☑	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Hickey *et al.* 2017 US	Pilot case-control study (n=46) Case: Patients with sinus rhythm restored given KardiaMobile. ☑ Controls: Standard care (no daily ECG self-monitoring). ☑	Cases: adults aged 21 years or older with a documented history of AF, scheduled to undergo a cardioversion, ablation or medical management aimed at maintaining a normal sinus rhythm. Controls age matched (within five years), gender matched patients with a documented history of AF receiving usual cardiac medical care (no daily ECG self-monitoring) as part of usual clinical management. ☑ Setting: departments of cardiac electrophysiology and cardiac ambulatory care	AF and flutter detection, quality of life (SF-36v2), patient satisfaction, ease of use, hospitalisations, mortality. ☒☑	Composite outcome (AF and atrial flutter)

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Hickey *et al.* 2013 US	Case report (n=1) Intervention: KardiaMobile (provided to patient after second cardioversion) ☑	Patient with history of AF, who had previously undergone two ablations and one cardioversion. ☑ Setting: inpatient	A&E attendance, change in medication. ☒☑	Healthcare provider review of KardiaMobile trace instructed patient to attend nearest emergency room
Carlson *et al.* 2016 US	[Abstract] Cohort (n=13) Intervention: KardiaMobile (patients instructed to take recordings twice daily for first two weeks, and monthly thereafter, or when symptomatic) ☑	Consecutive patients with iPhones who underwent AF ablation. ☑ Setting: inpatient	Number of ECG recordings, AF and atrial tachycardia detection, time to diagnosis, time to treatment ☑	Combined AF with atrial tachycardia.

Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope.

Abbreviations: AF atrial fibrillation; AHA American Heart Association; HRQoL health-related quality of life; RCT randomised controlled trial;

Table 4c: Studies selected by the EAC as the evidence base: population included patients with AF diagnosed to assess AF burden

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Guhl *et al.* 2020 US [AF-LITT study; NCT03093558]	RCT (single-centre) computer generated; powered to detect difference in AFEQT score (HRQoL specific to AF). Intervention (n=61): relational agent (providing health education, monitoring and problem-solving for patients) and KardiaMobile. Participants instructed to use daily. ☒☑ Control (n=59): Standard care (assumed no intervention) ☑	Patients aged 18 years or older, history of chronic AF, prescribed oral anticoagulation for stroke prevention secondary to AF, English speaking sufficient to use a smartphone-based relational agent. ☑ Setting: ambulatory centre	Quality of life, patient adherence to intervention, acceptability. ☑	Subsequent to pilot published by Magnani *et al*. 2017 (which was identified by the company). Mixed intervention, assessment of AF burden.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Praus *et al*. 2021 US	Single-arm observational (n=43) Intervention: KardiaMobile-1L (interpreted by nurse practitioner) and NowClinic (telehealth platform). Patients instructed to send daily readings and whenever symptomatic ☒☑	Adult patients who had two or more AF-related emergency department or urgent care visits in last 12 months, needed rate control with medication titration, or needed monitoring of AF reoccurrence after re-establishing sinus rhythm (chemically or direct current cardioversion). ☑ Setting: Clinic	Patient satisfaction, ease of use, quality of life, emergency department visits, hospitalisations, unclassified recordings ☑	Mixed intervention, single-arm

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Gupta *et al.* 2020 US	[Abstract] RCT (n=96) Intervention: KardiaMobile (recorded five times per week) ☑ Control: Standard care	Patients with AF with CHA_2DS_2-VASc score of 2 or more, eligible for anticoagulation and had a smartphone. All patients received six months of anticoagulant (apixaban) dispensed as one-month pre-loaded pill boxes. ☒☑ Setting: not reported	Medication compliance, device compliance, number of recordings, adverse events (related to anticoagulation) ☒☑	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Javed *et al.* 2019 [Country not reported]	[Abstract] Diagnostic accuracy (n=29) Reference test: Two physicians' interpretation of KardiaMobile ECG. Index test: KardiaMobile (instructed to take recording every day, and when experiencing symptoms, median follow-up 20 months) ☑	Patients with paroxysmal AF and low CHADS2-VASc score. ☑ Setting: not reported	Patient compliance, diagnostic accuracy, undetermined ECGs (assumed to be unclassified) ☑	
Scales *et al.* 2020 US	[Abstract] Cohort (n=18) Intervention: KardiaMobile (for three weeks) ☑	Recent AF related emergency department or outpatient clinic visit, with new prescription for a rate control medication. ☒☑	Number of recordings, heart rate (compared with baseline measurements), emergency room visits or unplanned hospitalisation. ☒☑	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Ross *et al.* 2016 US [Abstract by Smith *et al.* 2016 appears to report on the same patient group but different outcomes]	[Abstract] Cohort (pilot) (n=18) Intervention: KardiaMobile (patients instructed to record twice daily for three months, and to make no therapeutic changes based on monitoring data but invited to contact their heart rhythm clinicians in the event of AF detection or adverse symptoms) ☑	Patients with paroxysmal AF and rhythm control management ☑ Setting: Not reported	AF detection, patient adherence to recording twice daily [Smith *et al.* 2016 (n=17) quality of life] ☑	

Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope.

Abbreviations: AF atrial fibrillation; AFEQT Atrial Fibrillation Effect on Quality of Life; ECG electrocardiogram; HRQoL health-related quality of life; RCT randomised controlled trial;

Table 4d: Studies selected by the EAC as the evidence base: population included patients with transient AF post-surgery or hospitalisation who reverted back to sinus rhythm prior to discharge

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Lowres *et al.* 2016 Australia [ACTRN12614000383662]	Single-arm observational (feasibility study, multi-centre, n=42) Intervention: KardiaMobile-1L (participants instructed to take recording four times a day, or when symptomatic, for four weeks), symptom diary ☑	Adults aged 18 years and over, who had transient AF following cardiothoracic surgery (with no history of AF prior to admission), and stable sinus rhythm achieved (reverted or cardioverted) before discharge. ☑ Setting: tertiary teaching hospital and private hospital	Recurrence of AF, diagnostic accuracy (automated software detection compared to cardiologist interpretation), patient compliance, ease of use ☑	Interpretation by cardiologist included 12-lead ECG and Holter where available.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Lowres *et al.* 2020 Australia [ACTRN12616000904471]	Single-arm observational (feasibility study; multi-centre)(n=29) Intervention: KardiaMobile-1L (participants instructed to use three times daily or when symptomatic for four weeks commencing from hospital discharge) and symptom diary ☑	Patients aged 18 years or older with an episode of new-onset AF secondary to hospitalisation for either non-cardiac surgery or non-cardiovascular acute medical illness. Eligible if admitted to hospital in sinus rhythm with no prior history of AF, and reverted to sinus rhythm prior to discharge (spontaneously or via cardioversion). ☑ Setting: tertiary hospitals	Recurrence of AF, time to recurrence, patient compliance, ease of use. ☑	Single-arm; included in adverse events only

Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope.

Abbreviations: AF atrial fibrillation; ECG electrocardiogram;

Table 4e: Studies selected by the EAC as the evidence base: population included patients post-stroke or TIA

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Koh *et al.* 2021 Malaysia [SMART-AF study; NCT04332718]	RCT (multi-centre); computer-generated randomisation. Intervention (n=105): 30-day KardiaMobile ☑ Control (n=98): additional round of 24-hour Holter monitor	Patients aged 55 years and above, without known AF, with ischaemic stroke or TIA within previous 12 months. Standard work-up conducted: 12-lead ECG, 24-hour Holter monitoring, inpatient telemetry ECG monitoring, brain and neurovascular imaging, and TTE. Patients excluded if the most likely etiologic diagnosis had been determined, if unable to use KardiaMobile on a smartphone or if life expectancy was less than one year. ☑ Setting: ambulatory	Diagnostic yield within three months, oral anticoagulation☑	Published after clinical submission by company, supersedes abstract identified by the company.
Yan *et al.* 2020 Australia and China/Hong Kong	Single-arm observational (multi-centre)(n=1,079) Intervention: KardiaMobile-1L	Patients hospitalised for stroke or TIA without history of AF and no AF on admission 12-lead ECG. Excluded if treating	AF detection, time to detection, proportion of patient's anticoagulated at three months. ☑	Single-arm; included in adverse events only

	recording performed by nursing staff during routine observations (typically every two to four hours) interpreted by physician. All patients received 12-lead ECG. Holter monitoring was at the discretion of stroke team. ☑	medical team considered long-term oral anticoagulation use inappropriate because the stroke was very severe or in light of other comorbidities. ☑ Setting: stroke unit		
Philip *et al.* 2016 India	[Abstract] Cohort (n=129) Intervention: daily screening with KardiaMobile. All patients also had 24-hour Holter monitor. Patients noted to have AF on KardiaMobile were confirmed with 12-lead ECG immediately. ☑	Acute ischaemic stroke patients. ☑ Setting: inpatients	AF detection ☑	Only those with AF detected on KardiaMobile had 12-lead ECG.
Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope. Abbreviations: AF atrial fibrillation; ECG electrocardiogram; RCT randomised controlled trial; TIA transient ischaemic attack; TTE transthoracic echocardiogram				

Table 4f: Studies selected by the EAC as the evidence base: KardiaMobile used in mixed population including patients with known or expected AF

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Selder *et al.* 2019 Netherlands	Diagnostic accuracy (n=233) Reference test: KardiaMobile with classification of ECG by study team ☑ Index test: KardiaMobile with classification of the ECG by the KardiaMobile algorithm ☑ [Patients instructed to use when experiencing palpitations or related complaints]	Typically, patients presenting with paroxysmal AF, palpitations of unknown origin or near-collapse were selected by the cardiologists of this clinic to participate in the Hartwacht program, although indications for inclusion in the program were left at the discretion of the physician ☒☑ Setting: private outpatient cardiology clinic	Diagnostic accuracy, unclassified, unreadable ☑	Potential inclusion of mixed population (have included people who may not have had AF or palpitations due to "discretion of physician")
Bray *et al.* 2021 UK	Single-arm observational (single-centre) Intervention (n=74): KardiaMobile over a six month period ☑	Hospital discharges of newly treated AF with rapid ventricular response rates referred to the Acute Community Team requiring monitoring and management, and patients with suspected	AF detection, number of recordings per patients, and if further 12-lead ECG was required, ease of use ☑	Mixed population (management of known AF, and diagnosis of new AF). Acute Community Team members took measurements, which may not be generalisable to the general public.

		AF due to abnormal pulse on manual pulse check. There were no specific exclusion criteria. ☑		
Lambert *et al.* 2019 **US**	[Abstract] Cohort (n=81) Intervention: KardiaMobile over (455 patient months of follow-up) ☑	Patients with known or suspected AF ☑ Setting: Cleveland Clinic	Number of ECG recordings, changes to management ☑	
Key: ☑ aspect of study in scope; ☒ aspect of study in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope. Abbreviations: AF atrial fibrillation; ECG electrocardiogram;				

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC considered 32 studies, including:

- 7 randomised controlled trials (2 RCTs were reported in abstract form only),
- 7 diagnostic accuracy studies (3 in abstract form only),
- 1 case-control study,
- 16 single-arm observational studies (9 in abstract form only), and
- 1 case report,

Five studies reported results from the iHEART study (investigating AF recurrence after AF ablation or cardioversion): Caceres *et al.* 2020, Goldenthal *et al.* 2019, Turchioe *et al.* 2019; Reading *et al.* 2018, Reading *et al.* 2017. Two additional studies report on same cohort (patients with paroxysmal AF and rhythm control management); Smith *et al.* 2016, Ross *et al.* 2016. The combined evidence includes KardiaMobile use in 2801 patients. None of the included studies explicitly mention of the use of KardiaMobile-6L. Recruitment of patients occurred in a variety of settings: emergency departments, outpatient clinics, cardiology departments, inpatients, with only one study conducted in a community setting.

The four peer-reviewed RCTs were conducted in different populations, comparing KardiaMobile with 'standard care' (where definition of standard care varied between studies) with different lengths of follow-up (ranging from 30 days up to 6 months). Reed *et al.* (2019) compared KardiaMobile in addition to standard care (n=124), with standard care alone (which varied across 10 UK centres), in patients presenting to emergency departments with palpitations. Goldenthal *et al.* (2019) compared KardiaMobile (n=115) with standard care (no additional detail provided) to detect continuing AF in

patients who were treated for AF with radiofrequency ablation or direct current cardioversion. Health-related quality of life in this population was also reported by Caceres *et al.* (2020). Koh *et al.* (2021) compared 30-day KardiaMobile monitoring (n=105) with a standard repeat round of 24-hour Holter monitoring, for diagnosis of AF in patients with previous ischaemic stroke or TIA who had already had 12-lead ECG and 24-hour Holter monitoring. Guhl *et al.* (2020) compared KardiaMobile plus health advice given by a computerised relational agent (n=61) with standard care, in patients with chronic AF, to assess quality of life and AF burden.

The four peer-reviewed diagnostic accuracy studies used different reference standards, length of follow-up ranged from 14 days to 14 months. The largest (n=226) was a partial comparison, using the same ECG but comparing the KardiaMobile classification to clinical interpretation (Selder *et al.* 2019). William *et al*. (2018) compared KardiaMobile with 12-lead ECG in 52 patients. Narasimha *et al.* (2018) compared cardiologist interpretation of the simultaneously recorded KardiaMobile ECG traces and external loop recorder traces of 33 patients with undiagnosed palpitations. Hermans *et al.* (2021) compared researcher interpretation of KardiaMobile ECGs to 3 rounds of Holter monitoring in 33 patients in the 12 months following ablation treatment for AF.

The case-control study reported on 23 patients using KardiaMobile once per day or when symptomatic, and 23 age and gender matched patients (with no daily ECG monitoring), to detect AF recurrence, following cardioversion, AF ablation or medical management aimed at maintaining sinus rhythm (Hickey *et al.* 2017).

Seven peer-reviewed single-arm observational studies described the use of KardiaMobile for between 4 weeks and 16 months. The largest study (n=1,079) was in patients hospitalised for stroke or transient ischaemic attack with no history of AF (Yan *et al.* 2020). Dimarco *et al.* (2018) had the longest follow-up and included 148 patients referred to a cardiology due to intermittent palpitations. Reed *et al.* 2021 included 50 patients attending the emergency department with palpitations. Praus *et al.* (2021) used KardiaMobile to monitor

AF recurrence in 43 patients with a history of AF who had re-established sinus rhythm (chemically or with direct current cardioversion). Lowres *et al.* (2016; 2020) conducted two studies to detect AF recurrence within four-weeks in patients with transient (secondary) AF which reverted to sinus rhythm before discharge, following cardiothoracic surgery (n=42), or hospitalisation for non-cardiac surgery or a non-cardiovascular acute medical illness (n=29). Bray *et al.* (2021) followed a mixed population in a community setting including patients discharged from hospital with newly treated AF with rapid ventricular response, and patients with suspected AF due to an abnormal pulse.

Hickey *et al.* (2013) is a case report of a single patient, which described the use of KardiaMobile to detect AF recurrence in a patient with history of AF, following their second cardioversion.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

Four randomised controlled trials were critically appraised using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins *et al.* 2011). These appraisals are reported fully in Appendix B1, and summarised in Table 5. All four RCTs were considered moderate quality. Neither the patient nor the ECG interpreter could be blinded to use of the KardiaMobile device or its output, which risked performance and detection bias, although the EAC recognises that this lack of blinding is unavoidable. Two RCTs were powered to detect an increase in AF detection rate; Koh *et al.* (2021) aimed to detect a 9.5% difference in AF detection between arms, and Reed *et al.* (2019) aimed to detect a 15% increase in symptomatic rhythm detection. Goldenthal *et al.* (2019) aimed to detect a hazard ratio of 2 for detecting AF recurrence and Guhl *et al.* (2020) aimed to determine a mean 12 point improvement in HRQoL.

Table 5: Cochrane risk of bias for included RCTs

Study	N*	A	B	C	D	E	F	G	Overall quality**
Goldenthal *et al.* 2019	262	☺	☺	☹†	☹†	☺	☺	☺	Moderate
Reed *et al.* 2019	243	☺	☺	☹†	☹†	☺	☺	☺	Moderate

Guhl *et al.* 2020	120	☺	?	☹†	☹†	☺	☺	☺	Moderate
Koh *et al.* 2021	236	☺	☺	☹†	☹†	☹	☺	☺	Moderate

Key: ☺, low risk of bias, ☹, high risk of bias; ?, unclear risk of bias.
A, random allocation sequence (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome bias (attrition bias); F, selective reporting (reporting bias); G, other bias (for example industry involvement in finding, major concerns over generalisability. As domain G is particularly subjective and partly dependent on journal editorial policy, it is not used in overall summary of evidence.
* Total number of patients randomised.
** Overall summary of study quality (consistent with GRADE methodology):
High: Five or six domains A to F at low risk of bias or no high risk of bias in any single domain.
Moderate: high risk of bias in at least two domains (A to F) and low risk of bias in at least three domains (A to F).
Low: high risk of bias in three or more domains (A to F).
† high risk of bias but blinding of intervention not possible

Four diagnostic accuracy studies were critically appraised using the QUADAS-2 checklist. These appraisals are reported fully in Appendix B2, and summarised in Table 6. A different reference standard was used in each case (12-lead ECG, professional interpretation of the KardiaMobile ECG, event monitoring, Holter monitoring). Three studies compared KardiaMobile and clinical interpretation of the same ECG trace (Selder *et al.* 2019; Hermans *et al.* 2021; William *et al.* 2018). Two studies recorded the reference and index tests simultaneously (Narasimha *et al.* 2018, Selder *et al.* 2019), whilst William *et al.* (2018) recorded them consecutively. Hermans *et al.* (2021) conducted reference and index tests at different time points; using Holter monitoring for at least 24 hours after 3, 6 and 12 month follow-up appointments, and KardiaMobile for four weeks after only one of these follow-up appointments. Selder *et al.* (2019) was the largest diagnostic accuracy study, but as patient selection was at the discretion of the physician, the population was mixed.

Table 6: QUADAS-2 assessment of diagnostic accuracy studies.

Study	**Risk of bias**				**Applicability concerns**		
Patient selection	**Patient Selection**	**Index test**	**Reference standard**	**Flow and timing**	**Patient Selection**	**Index test**	**Reference standard**
Narasimha *et al.* 2018	High	Low	Low	High	Low	Low	Low
William *et al.* 2018	High	Low	Low	Unclear	Low	Low	Low
Selder *et al.* 2019	Unclear	Low	High	Low	Unclear	Low	Low

Hermans *et al.* 2021	High	Low	Unclear	Low	Low	Low	Low

The case-control study was critically appraised using the STROBE case-control checklist, Appendix B3. Patients in the KardiaMobile arm were sent educational messages which may have influenced patient behaviour (and potentially study outcomes) and could limit generalisability. The study reported an aggregated outcome, combining detection of AF and atrial flutter, but patients were followed for six months, and Kaplan-Meier analysis was conducted.

Seven single-arm observational studies were critically appraised using the STROBE cohort checklist, Appendix B4. In the largest (n=1,079, Yan *et al.* 2020), nursing staff took KardiaMobile recordings alongside their routine observations, which may limit generalisability when the device is used by patients without clinical support available. Three observational studies were in a UK setting (Bray *et al.* 2021; Dimarco *et al.* 2018; Reed *et al.* 2021), including the only study in a community setting (Bray *et al.* 2021). No study addressed confounding via multivariate analysis or stratification. Only Lowres *et al.* (2016) accounted for missing data by applying missing-at-random analysis.

The case report by Hickey *et al.* 2013 was not critically appraised.

The 14 studies only available in abstract form were not critically appraised. However, they have been included in the assessment due to their value in demonstrating longitudinal use, device acceptability and ease of use. The studies recruited sample sizes from n=13 (Carlson *et al.* 2016) to n=129 (Philip *et al.* 2016). Follow-up was until discharge (Philip *et al.* 2016) to a median of 20 months (Javed *et al.* 2019). Two abstracts described an RCT (Gupta *et al.* 2020; Turchioe *et al.* 2019) and two described diagnostic accuracy studies (Javed *et al.* 2019; Goel *et al.* 2018). One single-arm observational study compared heart rate recorded using KardiaMobile before and after three-weeks of rate control medication (Scales *et al.* 2020).

5.3 *Results from the evidence base*

The EAC cross-tabulated the 32 included studies against the outcomes listed in the final scope (NICE, 2021), Table 7.

Table 7: Cross-tabulation of included studies against outcomes.

				Outcomes															
	Study design	No. of patients using Kardia Mobile	Patient group	Diagnostic yield	Diagnostic accuracy	Time to first or recurrent AF event	Time to AF diagnosis or rule out	Time to initiation of treatment	Rate of test failure (Non-interpretable)	Rate of fail to classify (Not classified)	Total no. of outpatient appointments	Hospital admission	No. of visits to GP or urgent care	No. of further test in addition to KardiaMobile	Morbidity*	Mortality	Ease of use	Device acceptability and satisfaction	Health-related quality of life
Reed *et al.* 2019	RCT	124	palpitations	☑		☑					☑	☑	☑		☑	☑	☑	☑	
Goel *et al.* 2018	DA[#]	50	palpitations	☑															
Narasimha *et al.* 2018	DA†	33	palpitations	☑	☑												☑	☑	
Dimarco *et al.* 2018	SA	148	palpitations	☑			☑		☑									☑	
Onwordi *et al.* 2016	SA[#]	70	palpitations	☑														☑	
Reed *et al.* 2021	SA	50	palpitations	☑															
Frey *et al.* 2020	SA[#]	20	palpitations	☑														☑	
Goldenthal *et al.* 2019	RCT[&]	115	AF recurrence	☑		☑		☑				☑	☑					☑	
Caceres *et al.* 2020	RCT[&]	115	AF recurrence	☑															☑
Turchioe *et al.* 2019	RCT[&#]	115	AF recurrence	☑													☑	☑	
Hermans *et al.* 2021	DA†ǂ	115	AF recurrence	☑	☑				☑	☑							☑	☑	
William *et al.* 2018	DA†ǂ	52	AF recurrence		☑					☑							☑	☑	☑
Hickey *et al.* 2017	CC	23	AF recurrence	☑								☑				☑	☑	☑	☑
Reading *et al.* 2018	SA[&#]	50	AF recurrence	☑		☑													

Reading *et al.* 2017	SA[&#]	50	AF recurrence															☑	
Carlson *et al.* 2016	SA[#]	13	AF recurrence	☑			☑	☑										☑	
Hickey *et al.* 2013	CR	1	AF recurrence										☑						
Guhl *et al.* 2020	RCT	61	AF burden															☑	☑
Gupta *et al.* 2020	RCT[#]	46	AF burden															☑	
Javed *et al.* 2019	DA[#]	29	AF burden		☑					☑								☑	
Ross *et al.* 2016	DA[#]	18	AF burden	☑														☑	
Praus *et al.* 2021	SA	43	AF burden	☑					☑	☑		☑	☑				☑	☑	☑
Scales *et al.* 2020	SA[#]	18	AF burden										☑					☑	
Smith *et al.* 2016	SA[$#]	17	AF burden																☑
Lowres *et al.* 2016	SA	42	tAF	☑	☑												☑	☑	
Lowres *et al.* 2020	SA	29	tAF	☑		☑											☑	☑	
Koh *et al.* 2021	RCT	105	stroke or TIA	☑		☑				☑									
Yan *et al.* 2020	SA	1079	stroke or TIA	☑		☑													
Philip *et al.* 2016	SA[#]	129	stroke or TIA	☑															
Selder *et al.* 2019	DA†ǂ	233	mixed		☑				☑	☑									
Lambert *et al.* 2019	SA[#]	81	mixed															☑	
Bray *et al.* 2021	SA	74	mixed	☑										☑				☑	

Abbreviations: AF atrial fibrillation; CC case-control study; CR case report; DA diagnostic accuracy study; RCT randomised controlled trial, SA single-armed observational study; tAF transient AF; TIA transient ischaemic attack

Key:

*Morbidity including stroke, thromboembolism, heart failure, complications associated with preventative treatment;

† KardiaMobile trace interpreted by a clinician;

ǂ KardiaMobile trace interpreted by Kardia app;

[&]Reporting on iHEART cohort (different outcomes);

[$]Same population as Ross *et al.* 2016, however different outcomes reported;

[#]available in abstract only

Diagnostic accuracy

Five studies reported on diagnostic accuracy of AF detection, four of which used clinical interpretation of the KardiaMobile ECG as the reference standard with reported per-recording sensitivity ranging between 92% and 99%, and per-recording specificity between 92% and 98%, Table 8. However, it is important to note that repeated ECG measurements from an individual patient are not independent. Therefore the sensitivity and specificity reported in these studies should be interpreted with caution as they do not represent the diagnostic accuracy of KardiaMobile in diagnosing AF *per patient.* Additionally these studies were conducted across four different patients populations (undiagnosed AF, AF recurrence post-treatment, transient AF following cardiac surgery, known paroxysmal AF measuring AF burden) with a different pre-test probability of AF; ranging between 4.8% to 35.6%.

Table 8: Diagnostic accuracy of the Kardia app classification in detection of AF

Study	No. patients	Population	Index test (no. of recordings)	Reference standard (no. of recordings)	Per-recording prevalence of AF	Sensitivity	Specificity	Diagnostic accuracy
Selder *et al.* 2019	233	Mixed population	Kardia app interpretation (n=5,982)	Study team interpretation (n=5,982)	19% (1,135/5,982)	92%	95%	94%
Hermans *et al.* 2021	115	AF recurrence post-treatment	Kardia app interpretation (n=7,838)	Study team interpretation (n=7,838)	7.9% (622/7,838)	95.3%	97.5%	NR
William *et al.* 2018	52	AF recurrence post-treatment	Kardia app interpretation (n=161; 62 unclassified and 2 uninterpretable removed)	Interpretation of 12-lead ECG (n=161; 62 unclassified and 2 uninterpretable removed)	35.6% (80/225)	96.6%	94.1%	NR
Lowres *et al.* 2016	42	Transient AF (following cardiac surgery)	Kardia app interpretation (n=3,335)	Cardiologist interpretation (n=3,335)	NR (3,335 ECGs but number of AF confirmed not reported)	94.6% [95%CI 85.1% to 98.9%]	92.9% [95%CI 92.0% to 93.8%]	NR
Javed *et al.* 2019	29	AF burden (known paroxysmal AF)	Kardia app interpretation (n=14,998)	Physician interpretation (n=14,998)	4.8% (715/14,998)	99% (99% when unclassified traces were regarded as possible AF)	98% (87% when unclassified traces were regarded as possible AF)	NR
Abbreviations: AF atrial fibrillation, CI confidence interval, ECG electrocardiogram, NR not reported								

Diagnostic yield

Six comparative studies (three RCTs, two diagnostic accuracy and one case-control study) and one observational study reported that KardiaMobile detected AF more frequently than 'standard care'; the definition of standard care varied by study, Table 9.

Table 9: AF detection across seven studies.

Study (year); study design	Patient population	Definition of standard care	AF detection in intervention arm	AF in comparator arm
Reed *et al.* (2019); RCT	Undiagnosed palpitations	Varied by centre, included: Holter (24-hour, 48-hour, 7+ days), subsequent ECG (at emergency department or GP)	6.5%	0%
Narasimha *et al.* (2018); Diagnostic accuracy	Undiagnosed palpitations	External loop recorder (monitoring duration between 14 and 30 days)	18.2%	12.1%
Goldenthal *et al.* (2019); RCT	AF recurrence after treatment	Not defined	50.4%	41.5%
Hermans et al. (2021); Diagnostic accuracy	AF recurrence after treatment	Holter (min 24-hour) repeated at 3, 6 and 12 months.	25.2%	14.8%
Hickey *et al.* (2017); Case-control	AF recurrence after treatment	Usual cardiac medical care (no daily ECG self-monitoring)	60.9%	30.4%
Koh *et al.* (2021); RCT	Post-stroke or TIA	Additional round of Holter (24-hour)	9.5%	2.0%
Yan *et al.* (2020); Observational study	Post-stroke or TIA	Holter (24-hour)	8.8%	Not reported

Abbreviation: AF atrial fibrillation; TIA transient ischaemic attack

However, diagnostic yield depends on the frequency and duration of KardiaMobile use, and how per-patient positive cases are defined (whether clinical interpretation is used); repeated measurements from patients with KardiaMobile will cause sensitivity to tend towards 100% and specificity to tend towards 0%.

Reed *et al.* (2019) confirmed that a higher number of patients presenting at emergency care with palpitations had a cardiac arrhythmia detected within 90 days when using KardiaMobile, when compared to standard care, which included Holter monitoring at some centres (risk ratio 10.3 [95%CI 1.3 to 78.5], p=0.006). Goldenthal *et al.* (2019) reported that KardiaMobile identified more patients with AF or flutter recurrence (post-treatment) than standard care (Cox proportional hazard ratio 1.56 [95%CI 1.06 to 2.30], p=0.024). Hickey *et al.* (2017) reported the same outcome with a hazard ratio of 2.55 [95% CI 1.06 to 6.11], p=0.04. Koh *et al.* (2021) reported higher detection of at least one episode of AF lasting 30 seconds or longer, using KardiaMobile, when compared to 24-hour Holter monitoring (9.5% versus 2.0%, p=0.024) in patients being monitored with a previous ischaemic stroke or TIA. Higher detection of AF with KardiaMobile was also reported in the diagnostic accuracy study by Narasimha *et al.* (2018) (18.2% versus 12.1% in per-protocol analysis; statistical significance of this difference in proportion is not reported), when compared to ELR in patients presenting with palpitations.

Yan *et al.* (2020) reported on 294 patients who had Holter monitoring in addition to KardiaMobile, at the discretion of the hospital. KardiaMobile detected AF in 25 patients, and Holter monitoring detected AF in eight patients, one of which was not identified by KardiaMobile.

Time to AF detection

Two RCTs (Reed *et al.* 2019 and Goldenthal *et al.* 2019) and one observational study (Yan *et al.* 2020) reported that KardiaMobile reduced the time to AF detection when compared to standard care. Two observational studies (Lowres *et al.* 2020 and Dimarco *et al.* 2018) reported time to AF detection, but did not report comparative

results. Time to detection is influenced by how frequently patients submit KardiaMobile recordings, and also the frequency and time-interval at which the ECGs are reviewed by a healthcare professional to confirm AF detection or diagnosis.

Reed *et al.* 2019 demonstrated, in a study across ten UK emergency departments, that use of KardiaMobile in patients presenting with palpitations significantly reduced time to symptomatic cardiac arrhythmia detection, when compared with standard care (9.9 days versus 48.0 days, p=0.0004). Goldenthal *et al.* (2019) stated that cardiac arrhythmia recurrence following ablation or cardioversion was detected earlier with KardiaMobile when compared to standard care, but this was not quantified.

Yan *et al.* (2020) reported that the median time to AF detection using KardiaMobile (n=25) was three days [IQR 2 to 6], and was seven days [IQR 6 to 10] in those identified (n=8) by 24-hour Holter monitoring, p=0.02. Lowres *et al.* 2020 reported on 29 patients with new onset transient AF, of which KardiaMobile identified 12 with "potential AF" within a median of 6 [range 2 to 23] days. Ten of these sought medical advice and had confirmation of AF recurrence before their scheduled four-week follow-up appointment, resulting in a change to the management of 9 patients. Dimarco *et al.* (2018) reported that 8/148 patients with palpitations, monitored with KardiaMobile, were diagnosed with AF within a median of 12 [range 1 to 66] days.

Time to treatment

An abstract by Carlson *et al.* 2016 reported on 13 patients using KardiaMobile, and found that detected AF recurrence led to expedited cardioversion treatment. However, Goldenthal *et al.* (2019) reported a shorter time between detection and treatment in the control group than the KardiaMobile group (hazard ratio 0.33 [95% 0.57 to 2.92], p<0.0001), because fewer patients in the KardiaMobile group received treatment within the study period.

Morbidity

The RCT (n=240) by Reed *et al.* (2019) was the only study to monitor clinical outcomes during follow-up. This study reported one major cardiac event and one death within 90 days in the control arm, with none reported in the intervention arm.

However, with low numbers of events, the RCT would not have been powered to detect a difference in these outcomes between arms.

Unreadable ECG recordings

The Kardia app outputs "unreadable" to inform the patient when an ECG trace has interference and cannot be interpreted. Four studies explicitly reported the proportion of ECG traces deemed unreadable, ranging from 0.6% to 1.9%, Table 10.

Table 10: Studies reporting "unreadable" ECG recordings.

Study	Unreadable	Additional notes
Hermans *et al.* (2021)	0.6% (49/7838)	The research team was able to interpret 22.4% of these.
Praus *et al.* (2021)	0.7% (11/1501)	8 were uncategorised due to artefacts and 3 were too short
Selder *et al.* (2019)	1.7% (100/5982)	An independent cardiologist was able to interpret 8% of these
Dimarco *et al.* (2018)	1.9% (10/516)	

Failure to classify

The Kardia app outputs "unclassified" to indicate that the ECG trace is interpretable (that is, has no interference) but does not fit the classifications available. Six studies reported the proportion of recordings which were unclassified, Table 11, however no studies reported the proportion of patients. The company has confirmed that software updates have reduced the proportion of unclassified recordings over time.

Table 11: Summary of studies reporting the proportion of unclassified KardiaMobile electrocardiograms (ECGs).

Study	No of ECG	Proportion unclassified	Additional notes
Hermans *et al.* 2021	7,838	9.6%	Research team were able to give a diagnosis in 98% of unclassified cases.
Praus *et al.* 2021	1,501	11.5%	44% of the unclassified recordings came from two patients.

Koh *et al.* 2021	6,778	13.1%	Authors report that unclassified ECGs were mainly due to signal artefacts and the short duration of ECG recordings (less than 30 seconds); therefore it is unclear if the authors have combined unclassified and unreadable outcomes together.
Selder *et al.* 2019	5,982	17%	Independent cardiologist review of all ECG traces confirmed 2% were unclassified.
Javed *et al.* 2019	14,998	10.3%	No additional detail from abstract.
William *et al.* 2018	225	27.6%	Out of 62 unclassified recordings, 5 were non-interpretable by physician.

Hospital resource usage

Three comparative studies (RCTs by Reed *et al.* 2019 and Goldenthal *et al.* 2019; and case-control study by Hickey *et al.* 2017) and one observational study (Bray *et al.* 2021) reported on hospital resource usage. Reed *et al.* (2019) reported more emergency department attendances due to palpitations or pre-syncope with KardiaMobile in addition to standard care when compared to standard care alone (9.7% versus 2.6%, p=0.031). However, there were no significant differences in hospital admissions, outpatient appointments, GP attendances or ECGs performed due to palpitations or pre-syncope between intervention and control arms. Goldenthal *et al.* (2019) reported a non-significant increase in all-cause hospitalisation and emergency department attendance in the control arm (standard care), compared to the intervention arm (KardiaMobile with motivational text messages three times per week relating to management of AF and risk factors). Hickey *et al.* (2017) reported no difference in the rate of hospitalisations between intervention and control groups.

Bray *et al.* 2021, conducted in a primary care setting reported no cases required a 12-lead ECG due to the single-lead ECG not being sufficient for diagnosis.

Ease of use

A total of nine studies reported on the ease of use of KardiaMobile, Table 12.

Table 12: Summary of studies reporting on KardiaMobile ease of use.

Study	Outcome

Hermans *et al.* 2021	More patients found long-term intermittent KardiaMobile use more convenient than short-term continuous Holter monitoring.
Lowres *et al.* 2020	All patients reported that KardiaMobile was easy to use and that the time taken to record the ECG was not onerous.
Reed *et al.* 2019	87% found KardiaMobile easy to use.
Turchioe *et al.* 2019	Patients found the device easy to use and gave highest scores (on 5-point Likert scale) for device portability.
Narasimha *et al.* 2018	Patients reported (via questionnaire) that KardiaMobile was significantly easier to use than external loop recorder. Confirmed by higher compliance in KardiaMobile arm.
William *et al.* 2018	93.6% found KardiaMobile easy to use.
Hickey *et al.* 2017	During six months no patient had reported trouble using device.
Reading *et al.* 2017	52% of subjects needed frequent reminders (more than three) to transmit their ECG daily over the six-month monitoring period per protocol.
Lowres *et al.* 2016	95% found KardiaMobile easy to use. Only two participants reported they needed a familiarisation period. Shorter training was required for patients of higher education level and previous smartphone experience.
Abbreviations: ECG, electrocardiogram	

Ross *et al.* (2016) studied 18 patients advised to complete twice daily KardiaMobile recordings over three months, and found that adherence to twice-daily monitoring was suboptimal and declined over time (mean 76% in month 1, 56% in month 3). Narasimha *et al.* (2018) reported that one patient was unsuitable for inclusion, with resting tremors due to Parkinson's disease.

Patient satisfaction

Reed *et al.* (2019) reported that 56% of patients agreed or strongly agreed that KardiaMobile would be useful in diagnosing the cause of their symptoms. Hickey *et al.* (2017) reported that 92% of patients thought the device was beneficial. Lowres *et al.* 2020 found that 69% (11/16) of patients felt a sense of security from being able to self-monitor at home, and in another study, patients felt reassured on the absence of cardiac rhythm disturbance using KardiaMobile (Frey *et al.* 2020). William *et al.* 2018 and Praus *et al.* 2021 both reported that KardiaMobile reduced anxiety.

Quality of life

Five studies recorded quality of life, including the case-control study by Hickey *et al.* 2017, and two RCTs (Caceres *et al.* 2020 and Guhl *et al.* 2020), Table 13. Both RCTs used additional interventions, making it difficult to interpret the impact of

KardiaMobile in isolation. Caceres *et al.* 2020 included sending text messages regarding AF management once a week, and lifestyle factors and AF risk twice a week, for six months. Guhl *et al.* 2020 included a smartphone-based relational agent to simulate face-to-face counselling which also delivered AF education and symptom monitoring, and prompted rhythm monitoring.

Table 13: Studies reporting quality of life

Study	Study design	Quality of life outcomes
Caceres *et al.* 2020	RCT (n=238; Intervention: KardiaMobile, text messages and standard care, Control: standard care)	Comparing six month follow-up to baseline: • Both arms had improved AFEQT and AF symptom severity scores. • The global AFEQT score improved by 18.5 (SD 25.5) and 11.2 (SD 18.5) points in the intervention and control arms, respectively (p<0.05). • There were no statistically significant differences in HRQoL, quality-adjusted life-years, or AF symptom severity between groups.
Guhl *et al.* 2020	RCT (n=120; Intervention: KardiaMobile and relational agent, Control: standard care)	Comparing 30 day follow-up to baseline: • The intervention group had significantly higher improvement in total AFEQT scores (adjusted mean difference 4.5; 95% CI 0.6 to 8.3; p=0.03) than the control group. • Intervention group had significantly higher improvement in AFEQT daily activity sub-scores (adjusted mean difference 7.1; 95% CI 1.8 to 12.4; p=0.009) than the control group.
Hickey *et al.* 2017	Case-control (QoL assessed via SF-36v$_2$ only assessed in intervention arm, n=13)	Comparing six month follow-up to baseline: • Significant increase in physical component summary scores from 50.3 to 55.9 (p=0.02). • No significant increase in mental component summary scores from 47.5 to 51.7 (p=not reported).

Abbreviations: AF, atrial fibrillation; AFEQT, atrial fibrillation effect on quality of life; CI, confidence interval; HRQoL, health related quality of life; QoL, quality of life; RCT, randomised controlled trials.

Praus *et al.* 2021 assessed quality of life using the Hospital Anxiety and Depression Scale (HADS) in 31 patients pre-intervention and in 20 patients post-intervention, with no paired analysis reported. The abstract by Smith *et al.* (2016) reported no significant difference in quality of life (assessed by the Short Form Health Survey SF-36 and also AFEQT) in a cohort of 17 patients between baseline and three month follow-up.

6 Adverse events

Dimarco *et al.* (2018) was the only included study which included an adverse event directly attributable to the KardiaMobile device, where one patient returned the device due to an audible high-pitched noise. However, two studies commented on external factors impacting the ECG trace quality of KardiaMobile. Lowres *et al.* (2016) reported that the quality of ECG reading was impacted by movement artefacts and poor reception in rural areas. Selder *et al.* (2019) also reported artefacts being an issue in the older population, resulting in poor recording sensitivity (55%).

The EAC searched the US Manufacturer and User Facility Device Experience (MAUDE) database on 13/04/2021 (KardiaMobile, Kardia, AliveCor) and identified eight adverse events, (detail reported in Appendix C):

- Five cases where KardiaMobile classified the ECG as normal sinus rhythm but the patient had a heart attack (KardiaMobile is not intended to identify ST elevation)
- One false positive AF detection, which caused patient distress
- One patient's output displayed double their heart rate due to T-wave sensing
- One patient experienced frequent unclassified outputs from the Kardia app, which were thought to be due to low heart rate.

The company reported finding no adverse event reports for KardiaMobile (or AliveCor) in the UK Medicines and Healthcare products Regulatory Agency database, which the EAC verified (searched 13/04/2021).

7 Evidence synthesis and meta-analysis

No evidence synthesis was reported by the company. Due to heterogeneity in study design, populations in which KardiaMobile has been used, and different comparator and reference standards used, the EAC deemed that this was appropriate.

8 Interpretation of the clinical evidence

The clinical evidence base relating to KardiaMobile is heterogenous in terms of study design, patient population (with different underlying prevalence of AF), comparator or reference standard and setting; however this is reflective of how it would be used in an NHS setting. Five studies were conducted in a UK NHS setting, and described the use of KardiaMobile in a total of 466 patients. Four of these studies included patients with undiagnosed palpitations and one study included a mixed population (used for AF diagnosis and management); patients were aged from 7 years old, with one study reporting a mean age of 78.7 years.

Both RCT and real-world evidence demonstrate the increased diagnostic yield of KardiaMobile in detecting more AF and earlier when compared to standard care (including Holter monitoring, event recorders). The sensitivity and specificity of the Kardia app in detecting AF and AF recurrence, on a per-ECG recording basis, is high when compared to clinical interpretation of the KardiaMobile ECG trace. Furthermore, the automated detection software has developed over time, resulting in the introduction of additional categories, and reduction of the proportion of “unclassified” readings. However, as the instructions for use state that the KardiaMobile output cannot be used as a clinical diagnosis, the EAC recommends interpretation of all ECG traces by a qualified healthcare professional. This could be delivered through existing ECG monitoring and surveillance services, and would minimise risks associated with false negatives and false positives.

The EAC recognises there is no perfect reference standard for diagnosing paroxysmal AF; the clinical experts confirmed that a range of diagnostic monitoring tools are used for a variety of durations dependent on the patient characteristics, history, frequency and severity (with syncope being the most severe) of symptoms. KardiaMobile does demonstrate benefit in increased AF detection, and faster time to detection when compared to Holter monitoring and external loop recorder monitoring. The volume of real-world evidence included does demonstrate high patient compliance due to the ease of use, with potential benefits in increased quality of life.

There are no major safety concerns regarding KardiaMobile.

The EAC has examined the claimed benefits of KardiaMobile made by the company in the context of the clinical evidence included, Table 14.

Table 14: Summary of clinical evidence for claimed benefits

	Claimed benefits	EAC opinion
Patient benefit	Earlier diagnosis ordetection of AF leading to improved patient outcome	Benefit likely Two RCTs report that KardiaMobile reduced time to AF detection when compared to standard care. However, time to AF detection is influenced by how frequently patients are advised to use the device, and how quickly ECGs traces are subsequently reviewed by a healthcare professional. It seems plausible that earlier diagnosis leads to earlier treatment and better patient outcomes.
	Improved identification of people with AF leading to improved patient outcome	Benefit likely Five comparative studies (including 3 RCTs) report that KardiaMobile detected AF more frequently than standard care. However AF detection is influenced by the frequency and duration of KardiaMobile use. It seems plausible that increased AF detection leads to increased treatment and better patient outcomes.
	Improved patient compliance and data collection	Benefit likely Real-world evidence supports that KardiaMobile is easy to use. Limited evidence to suggest KardiaMobile results in improvements in quality of life (three comparative studies all included multiple interventions).

System benefits	Improved diagnostic yield minimising the number of repeat tests needed to confirm or rule out AF	Benefit likely Lead-I recordings from KardiaMobile-1L or KardiaMobile-6L can be interpreted by a clinician to diagnose AF in line with ESC guidelines. Unreadable traces occur in <2% of cases (some of which can be interpreted by a clinician).
	Improved diagnostic accuracy and efficiency in detecting AF in symptomatic and asymptomatic patients	Benefit likely Published evidence has included 6 broad patient groups, all with different underlying risk of AF. This heterogeneous patient mix is representative of NHS care.
	Avoiding unnecessary referral to secondary care	Benefit not proved One RCT reported an increase in ED attendances, but no significant differences in hospital admissions, outpatient appointments, GP attendances or ECGs performed between KardiaMobile and standard care. Another RCT found no significant differences in all-cause hospitalisation or A&E attendance between KardiaMobile and standard care. One study based in the community confirmed no cases required a 12-lead ECG for diagnosis.
	Ease of implementation minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas	Benefit likely No evidence directly supports this, however KardiaMobile ECG interpretation could take place within existing ECG monitoring services. Remote review of ECG by a healthcare professional is a benefit (particularly during pandemic), however one paper did explicitly state that ECG quality was reduced in patients living in rural area.
	Reduction in health service resource use such as staff in ambulatory ECG monitoring pathway	Benefit not proved The output of KardiaMobile cannot be used as a clinical diagnosis (as advised by device instructions for use), and requires clinical interpretation. Patients may also attend GP or emergency department if a “possible AF” output was received.

8.1 *Integration into the NHS*

The available evidence supports the use of KardiaMobile across a range of patient groups, in a range of settings. However there are significant barriers to adoption in some patient groups, including those with resting tremor, and those living in rural

areas. Additionally, KardiaMobile patients need a compatible internet-enabled phone or tablet, which may require consideration in an economic evaluation. Healthcare staff and patients may need limited training on downloading the app, and will need training to use the Heart Monitor and app in order to ensure a high-quality ECG trace. Training is also available within the Kardia app.

There are two versions of the KardiaMobile Heart Monitor available (single and 6-lead). Only the output from lead-I (in both versions) is used by the Kardia app to classify the ECG trace, however healthcare professional interpretation will use all leads available. For patients receiving KardiaMobile within the NHS, healthcare professional interpretation would take place within existing Holter or event monitoring surveillance services. The situation in which patients buy their own KardiaMobile directly is out of scope for this assessment, but the EAC notes that it may have an impact on NHS services when patients report to their GP or to A&E with a potentially abnormal reading.

The company has informed the EAC that the device is already extensively used in the NHS and is available on the NHS Supply Chain.

8.2 *Ongoing studies*

The company identified 15 ongoing studies. The EAC excluded seven of these (Appendix D1): two have already been published and included in the clinical evidence (Koh *et al.* 2021, Yan *et al.* 2020), one described the use of KardiaMobile in a screening population, one included patients with an implantable cardiac device (KardiaMobile is contraindicated in this group), one included KardiaBand (out of scope), one compared outputs from a smartwatch to KardiaMobile (comparator our of scope) and one could not be identified or retrieved by the EAC.

A total of 13 ongoing studies (eight identified by the company and an additional five identified by the EAC) are described in Appendix D2. None of the ongoing studies are based in the UK. The three largest ongoing trials (one observational study including 3000 patients, and two RCTs including 500 patients) are all set in the US, and have included KardiaMobile within a digital healthcare bundle making it difficult to measure the direct impact of KardiaMobile.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company conducted a separate literature search to identify economic evidence (Appendix E). This search strategy was almost identical to the company's clinical evidence search, with an additional 'economic' concept, covered by an appropriate range of terms. The EAC did not conduct a separate economic literature search, as all economic evidence would have been identified as a subset of the EAC's clinical evidence search.

The company identified five relevant studies, and summarised them in Table 1 of the Economic Submission, with individual details of each study reported in Section 2. One of these studies was available in abstract form only, did not include any formal cost analysis and was excluded by the EAC (Goel *et al.* 2018). The RCT by Halcox *et al.* (2017) was also excluded by the EAC as this was conducted in a screening population, which is out of scope for this assessment. The company did not draw overall conclusions from the published economic evidence. No parameters from the included economic studies informed the company's *de novo* model.

Published economic evidence review

The EAC critically appraised the three remaining published studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau *et al.* 2013), Appendix F1. A summary of identified economic evidence is given in Table 15.

Table 15. *Summary of economic studies identified.*

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
Praus *et al.* 2021 USA	Costing analysis added to a single-arm observational study recruiting from clinic. Cost reported in dollars.	Adult patients who had two or more AF-related emergency department or urgent care visits in last 12 months, needed rate control with medication titration, or needed monitoring of AF recurrence after re-establishing sinus rhythm (medically or direct current cardioversion).	Intervention (n=43): KardiaMobile-1L (interpreted by nurse practitioner) and NowClinic (telehealth platform). Patients instructed to send daily readings and whenever symptomatic	Patients were asked from where they would have sought care were the program not available (options: ED, UC, office visit or do nothing). Cost of emergency care visit.	11 patients avoided an emergency care visit, which would have resulted in total cost saving of $81,950.	Mixed intervention. Not generalisable to NHS. Appraisal in Appendix F1.
Reed *et al.* 2019 UK	Costing analysis added to an RCT that recruited from emergency department and acute medicine units. NHS reference costs used.	Participants aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythm during this episode remains undiagnosed after emergency department assessment.	Intervention (n=124 available for analysis): ECG recorded and analysed using KardiaMobile plus standard care. Control (n=116 available for analysis): Standard care only	Overall and median healthcare utilisation costs (primary, community care, secondary care and intervention costs) calculated for both groups.	Median overall healthcare utilisation cost in the intervention group (n=124) was £108 (IQR £99.0 to £246.50, range £99 to £2,697) versus £0 in the standard care group (n=116) (IQR £0 to £120.0, range £0 to £4,161; p=0.0001). Cost per symptomatic rhythm diagnosis was £921 less per patient; £474 in	Included symptomatic rhythms (not restricted to AF). Appraisal in Appendix F1.

					intervention group (n=69 patients with symptomatic rhythm) compared with £1,395 in the control group (n=11 patients with symptomatic rhythm).	
YHEC 2018 UK	Economic Impact Evaluation Case Study	Modelled a typical AF diagnostic pathway including two GP appointments, a 24-hour ECG, referral and follow-up outpatient appointment.	KardiaMobile pathway did not require a follow-up 12-lead, 24 hour or 7 day ECG to confirm diagnosis.	Cost of avoided healthcare appointments, and avoided cardiology investigations.	KardiaMobile saved £968 per patient by avoiding diagnostics and referrals to secondary care. Sensitivity analysis: if device was reused by multiple patients, there was a larger cost saving.	Appraisal in Appendix F1.
Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; ED, emergency care; GP, general practitioner; RCT, randomised controlled trial; UC, urgent care;						

Results from the economic evidence

The three published economic studies demonstrate the cost saving potential of KardiaMobile in terms of reducing healthcare appointments (emergency care, GP, ECG referral), Table 15. Two of the economic evaluations were from an NHS perspective.

The Reed *et al*. study randomised patients presenting to NHS emergency departments with palpitations or pre-syncope that remained undiagnosed after assessment in the Accident and Emergency department (A&E), to either standard care (n=116), or standard care plus KardiaMobile (n=124). Standard care varied across the ten tertiary and district general hospitals, however permuted block randomisation by site ensured this was taken into account. NHS reference costs from 2016/17 were used to calculate healthcare utilisation costs (including primary, community, and secondary care, and intervention costs), and the cost per symptomatic rhythm detected for both groups. The median costs were £108 (IQR from £99 to £246, range from £99 to £2,697) for the intervention group, and £0 in the standard care group (IQR from £0 to £120, range from £0 to £4,161; p=0.0001). The EAC considered that there was potential for bias in healthcare costs, this is due to local study team advising GP follow-up in cases where specialist follow-up of the ECG was *not* required, and thus increasing costs in the intervention arm only. The cost per symptomatic rhythm diagnosed was £921 less per patient in the intervention group (£474; n=69) compared with the control group (£1,395; n=11). However, this study, and the costs calculated, included all symptomatic rhythms (sinus rhythm, sinus tachycardia, ectopic beats, AF, supraventricular tachycardia, atrial flutter, sinus bradycardia, atrial tachycardia, ventricular tachycardia, and other rhythms). Therefore the EAC considers that KardiaMobile may provide additional healthcare benefits in supporting the detection or rule-out of other cardiac arrhythmias (however this is out of scope of this assessment).

The economic impact evaluation by the York Health Economics Consortium (YHEC) calculated the cost of a typical AF diagnostic pathway in the NHS including two GP appointments, one cardiology outpatient appointment, two cardiology follow-up appointments, a 12-lead ECG, a 24-hour ECG, and 7-day ECG. This was compared to the corresponding KardiaMobile pathway, which was assumed to include the full

cost of the KardiaMobile device (which intrinsically assumes each patient has a new device) and 2 GP appointments only. The KardiaMobile pathway (£171) saved £968 per patient investigated when compared with the typical pathway (£1,139), through fewer appointments and investigations. The EAC consider this cost saving as unlikely, as some patients on the typical pathway may receive a clinical diagnosis during the pathway and thus not require the full number of appointments and investigations included in this evaluation. The evaluation reported lower savings of £399 per patient when only 50% of patients required all of the tests in the typical AF pathway. Following the recommended clinical pathway for palpitations, KardiaMobile should be used after inconclusive 12-lead ECG, and may be used after Holter monitoring (increasing costs in the KardiaMobile arm). If KardiaMobile was adopted for 250 patients per year, the economic evaluation calculated total savings of £242,000 per year. Sensitivity analysis was also carried out, and found that £96,800 could be saved per year if only 100 patients followed the KardiaMobile pathway. The base case assumed that each KardiaMobile device was used by only one patient, but if the same device was used in a GP consulting room for 100 patients per year, this saving would rise to £106,601 per year. The EAC notes that using KardiaMobile for screening and single-time point testing is outside of the scope of the assessment, but recognises the potential for greater savings if the device is reused. The EAC notes that this evaluation only considers costs of appointments avoided during the diagnosis phase and does not consider cost of AF management and reduction in strokes, which would likely increase the cost saving associated with KardiaMobile.

9.2 *Company de novo cost analysis*

9.2.1 Economic model structure

The company developed a *de novo* model in an executable Excel spreadsheet, described across 20 worksheets. The EAC critically appraised the *de novo* model and its narrative description in the company Economic Submission using the Drummond checklist (Drummond et al. 1996), Appendix F2. The model included more than 150 parameters, 26 costs and 4 comparators. The model consisted of two separate Markov models representing an AF diagnosis phase (maximum 100 day duration using a 1 day cycle length) and subsequent management phase (five year duration using a one year cycle length). The diagnosis phase included repeat testing for inconclusive results (with a maximum of two repeats permitted in the model). A

series of embedded macros were used to conduct deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) for the base case. The company reported quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs).

The company provided an updated model on 12/05/2021 (EAC Communications Log, 2021). Changes to the model included:

- calculations used in the model to enable changes in AF prevalence,
- increase of the KardiaMobile costs (to reflect the KardiaMobile-6L device),
- calculations used to estimate AF rates in the Holter comparator arm,
- calculations used to estimate AF rates in the cardiac event recorder (CER) arm,
- additional labels were added to the calculations worksheet included in the model, and
- unnecessary data was removed from the calculations worksheet.

The company also provided an updated figure describing the structure of the model, illustrated in Figure 2. A third and final model was provided on 19/05/2021, as the company had highlighted that incorrect values were incorporated into the second version of the model (the hazard ratio experiencing myocardial infarction for novel oral anticoagulants (NOAC) and no treatment arms were inadvertently set to 0).

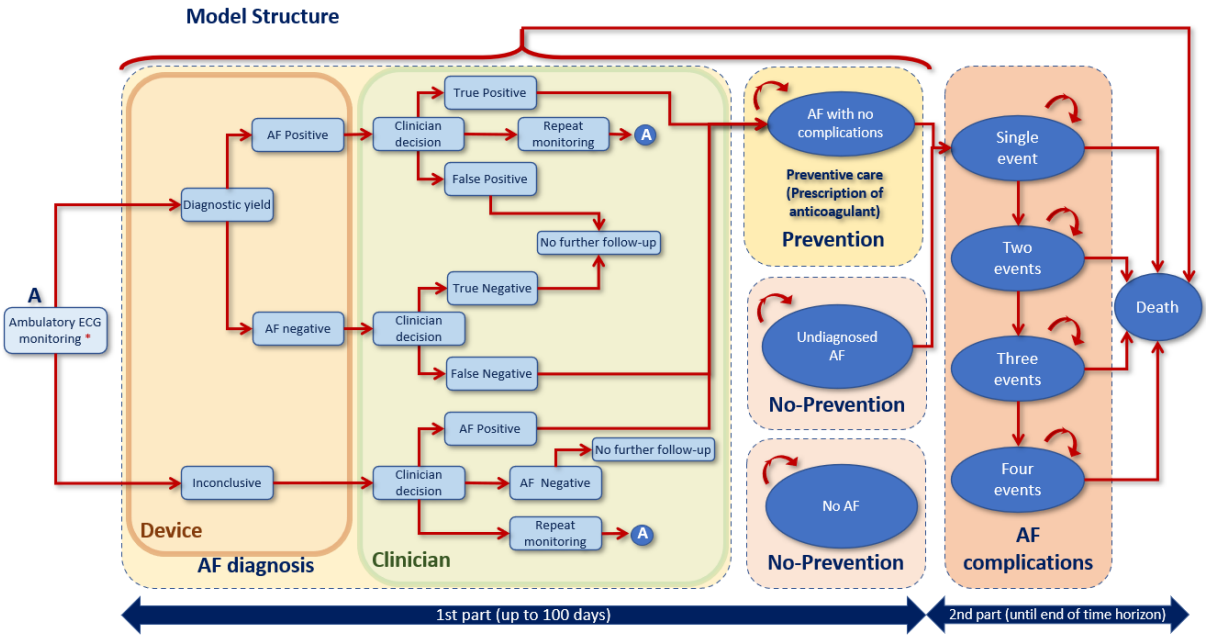
The EAC considered the model structure to be overcomplicated. The company confirmed that time dependent transitions in the diagnostic phase were introduced in order to model repeated monitoring and the faster time to AF diagnosis with KardiaMobile (EAC Communications Log, 2021). However the EAC felt that there was no robust evidence to support the need for such complex time dependencies in the diagnostic phase, that this approach required a number of additional assumptions and that the diagnosis phase could have been modelled more simply. For example, this could have been achieved by using a decision tree as in previous examples of AF diagnostic technologies which have been evaluated by NICE's

Medical Technologies Evaluation Programme (MTEP) (MTG52, 2020; MTG13, 2013).

The Markov states provided by the company in its illustration of the model (Figure 2) did not fully reflect the Markov states which were used in their calculations. For example, in the management phase, the "AF with no complications" state in the illustration was described by 4 separate states each representing AF with a single treatment (aspirin, warfarin, NOAC and no treatment); and the four "AF complications" states referred to as single, two, three, four events in the illustration were in fact represented by separate states for stroke, major bleed, intra-cranial hemorrhage and MI which could occur multiple times and in combination.

The layout of the spreadsheets was complex (assessed using the "Structure and Clarity" quality assurance (QA) section of the Business, Energy & Industrial Strategy (BEIS) Model Quality Assurance template). Inputs were split across multiple worksheets which made it difficult to trace the original sources of information. There were no hidden worksheets, however some parameter values and assumptions were not explicitly described in the company's Economic Submission. The EAC sent lists of questions to the company on two occasions to try to clarify understanding of the model. The company confirmed that more than a dozen values described in the Economic Submission were not applied, or were incorrect and differed from the actual values applied in the *de novo* model. The company provided the following explanation: *"Due to the volume of model parameters and the number of iterations of the model that were developed in the process of finalizing the submission, some parameters from old iterations of the model were inadvertently included in the final submission."* (EAC Communications Log, 2021).

Figure 2. *Structure of the company de novo model (updated version received by EAC 12/05/2021).*



Population

The company defined the population as "Adults (average starting age of 64 in the model) with known, or suspected AF who are referred for ambulatory ECG monitoring." Asymptomatic patients were excluded as out of scope in the Clinical Submission and therefore were correctly not included in the model. The average starting age includes a high-risk group. However, the EAC notes a wide population were included within the Clinical Submission (one study included a mixed population with a minimum age of 7, one community study had a mean age 78.7 years). The company confirmed that the age of 64 determined risk of death and had no influence on risk of AF or subsequent stroke (EAC Communication Log, 2021). The prevalence of AF was fixed at 30% and did not change during the diagnostic phase even when three rounds of monitoring were employed.

Intervention

The company included KardiaMobile (single or 6-lead Heart Monitor combined with the Kardia app). The model included functionality to assume KardiaMobile ECG

interpretation by the Kardia app and a clinician (base case, in line with instructions for use) or the Kardia app only (scenario analysis). The model included a 14-day monitoring period using KardiaMobile with a 3-day wait time for a diagnosis. However, the EAC noted from the model outputs that diagnosis and treatment in the KardiaMobile arm could occur on day one (violating this assumption). The company clarified that in the model all "possible AF" diagnoses from the KardiaMobile device were confirmed by clinician and started treatment on the same day. This assumption was not an editable input of the model, and not described in the Economic Submission. The clinical experts reported different time intervals between a patient emailing an ECG and it being reviewed: within one working day, three times weekly, once weekly, variable within centre. Another centre does not ask patients to email their ECGs but arranges a follow-up clinic appointment at the end of the monitoring period (ranging between 14 and 90 days); the expert stated that clinical ECG review, diagnosis and starting treatment would all occur at this follow-up appointment. One clinical expert stated that following discussion of a confirmed diagnosis with a patient, the clinical team would write to their GP to suggest treatment initiation. Two clinical experts estimated 1-2 weeks to initiate treatment, and another expert aimed to start treatment as soon as possible but mentioned delays if the patient could not be contacted by telephone. Therefore the EAC considers that a 3 day wait time is highly unlikely to be realistic reflection of current NHS practice; and highly unlikely that patients receiving a "possible AF" outcome from KardiaMobile would be diagnosed and treated on the same day.

The company modelled repeat monitoring for a small proportion of patients with an "inconclusive" result from any device, which the company later confirmed represents ECGs regarded as "unclassified" or "unreadable" by a clinician (EAC Communication Log, 2021). A maximum of 2 repeated sessions of monitoring were permitted in the model. The consensus from the clinical experts was that 2 repeated monitoring tests was unlikely, with one expert stating that they use only a single diagnostic test per patient. One expert stated that repeat testing was applicable across all patient subgroups.

Comparator

Multiple comparators were included by the company:

- Holter monitoring (24 hours)
- Holter monitoring (48 hours)
- Holter monitoring (7 days)
- Zio patch electrode monitor (14 days)

These comparators only represent the first round of testing modelled. Clinical experts confirmed that practice across the UK varies, however 24 hour was the most common duration of Holter monitoring reported. The EAC notes that there is no published evidence directly comparing the diagnostic performance of KardiaMobile to the Zio patch or implantable cardiac monitors, the latter of which was modelled for repeated monitoring only.

Repeated monitoring included a combination of devices and durations; cardiac event recording (CER, 30 days) and implantable cardiac monitors (no time limit defined in the model) were also included within costs of repeat monitoring, but not described explicitly as comparators in the Economic Submission. Three clinical experts reported variation in NHS practice, with duration of CER monitoring ranging between 7 and 30 days. Three clinical experts stated that implantable cardiac monitoring would be considered in patients with undiagnosed syncope or loss of consciousness, and three stated that low frequency (two or three times a year) or long duration between symptoms (more than two weeks) may require an implantable device. Only one expert stated that implantable devices may be used for suspected AF when undiagnosed by other devices, and another expert stated that implantable cardiac monitors were not used widely for AF diagnosis. The EAC recognises that patients eligible for implantable cardiac monitoring may have symptomatic episodes that are more than 14 days apart; limiting its value as a comparator to KardiaMobile in this *de novo* model.

Outcomes

The outcome of the diagnosis phase was the occupation of the following health states: AF with no complications, no AF, or undiagnosed AF. In the KardiaMobile arm only patients receiving a “possible AF” outcome from the Kardia app had a

follow-up clinic visit; however this functionality was editable in different scenarios of the model. In the comparator arm, monitoring for all patients was followed with an outpatient clinic visit; the company confirmed that this was not editable for comparators in the *de novo* model (EAC Communications Log, 2021).

In the model, those diagnosed with AF (using KardiaMobile or any comparator) received medication (aspirin, warfarin, NOAC or none) on the same day. All health states had transition probabilities to a series of adverse event states (captured during management phase). The outcomes of the management phase were the number of clinical adverse events (stroke, MI, intracranial haemorrhage, major bleed) and death (absorbing state). The annual risk of stroke in the "undiagnosed AF" group was modelled at 7.85%, which represents an annual risk of stroke between CHA_2DS_2-VASc scores of 5 and 6. The EAC considers this may be too high, particularly when used to represent a population presenting with *de novo* palpitations or pre-syncope and without other comorbidities.

Time horizon

The company used a maximum 100-day time horizon for the diagnosis phase; no justification for this duration was provided. As patients were diagnosed with AF they moved to the management phase. However, the time to diagnosis in the model did not use information from the clinical studies which reported on time to AF detection or time to treatment. The EAC considered that the way in which repeat monitoring was included within the diagnosis phase, with different devices and time-dependent probabilities, introduced unnecessary complexity and uncertainty (in costs, proportion of use, and time), which could have been simplified. The company clarified that repeated monitoring could be removed in the model as a scenario. The company used a 5-year time horizon for the management phase to capture long-term outcomes, with a 3.5% discount rate. The EAC considered this to be appropriate given the impact of diagnosing AF on reducing subsequent strokes, however other time horizons would also be applicable, including 1-year (to reflect NHS practice where patients have annual healthcare reviews which may detect AF) and 10 years (MTG13, 2013). The EAC notes that there was no published long-term evidence included in the company Clinical Submission which demonstrated reduction in strokes or mortality directly associated with the KardiaMobile device;

however considers it reasonable to make the assumption that increased detection in AF will result in these benefits.

9.2.2 Model assumptions

The principal assumptions made by the company were reported in Table 2 of the Economic Submission. The EAC has commented on the validity of these assumptions in Table 16. The EAC considered that some of these assumptions lead to bias in favour of KardiaMobile in the economic analysis.

Additional assumptions were made within calculations of the model but were not explicitly described in the company Economic Submission. Due to the complexity of the submitted model the EAC cannot be certain that all the assumptions were identified by the company or the EAC. For example, the EAC noted the following:

- The structure of the model was chosen by the company in order to account for time-dependency. However none of the clinical studies which reported time to AF detection or time to treatment (which were included in the company Clinical Submission) were included as inputs in the *de novo* model.

- All the results of the model follow from the diagnostic yield of the different AF monitoring devices. However the company determined the prevalence of AF (Sanna *et al.* 2014) and the proportion of patients with AF detected for each device using different sources (KardiaMobile and Holter, Hermans *et al.* 2021; Zio, Kaura *et al.* 2019; CER, Gladstone *et al.* 2014) which included different subgroups of patients. The company then calculated diagnostic yield in the model for each device using an incorrect and inconsistent approach, see Table 17.

- Repeat monitoring was applied in the model for patients with inconclusive results following the first round of Holter monitoring; split between 7-day Holter (90%) and 30-day CER (10%). However the diagnostic yield of Holter monitoring (24-hour, 48-hour and 7-day) applied in the *de novo* model was derived from the total number of patients with AF detected at one year from Hermans *et al.* 2019 study, which included 3 rounds of (24-hour minimum) Holter monitoring initiated at 3, 6 and 12 month follow-up outpatient appointments. Using this study as the source of diagnostic yield, the EAC

considers it inappropriate to include repeated Holter monitoring following a first round of Holter monitoring.

- No time or costs were included in model to account for ECG review by clinician for any device. The IFU states that the output from the Kardia app cannot be used as a clinical diagnosis; therefore all ECGs should be interpreted by a clinician. The EAC has assumed that this has been omitted deliberately as each device requires clinical interpretation, and that this effectively cancels out. However, two experts stated that the time required to review ECGs varies, with one expert stating times between 10 minutes and 60 minutes, depending on the technology and duration of monitoring. Clinical experts generally agreed that a tiered approach to ECG review was usual in NHS practice, with electrophysiologists or technicians conducting first review, and specialist arrhythmia nurses, GPs or cardiologists then reviewing those deemed abnormal. One expert stated that although their centre's ECGs are interpreted in-house, there are external services that provide interpretation for a charge. Additionally, with some patients requiring repeat monitoring in the company model the number of ECG reviews may vary. Furthermore, the cost of Zio service includes the interpretation and report (which has not been applied to the other arms of the company model). Following a request by the EAC, the company did confirm that ECG review time could be added to the nurse training time within the *de novo* model (EAC Communications Log, 2021). However this would introduce further bias, as ECG review time would not be added for the comparator arms.

Table 16. *Company's de novo model assumptions.*

Assumption	Company justification	Company source	EAC comment
All monitoring tests with Holter, Zio or continuous event recorder (CER) would be followed-up with an outpatient clinic visit (GP or specialist), regardless of findings.	Clinical expert opinion and based on information provided in NICE MTG52.	Clinical expert opinion NICE MTG52, 2020	The EAC disagrees with this assumption. MTG52 final guidance (section 4.9) reported that "Comments and clinical expert advice received at consultation suggested that an outpatient appointment would normally only be needed after a

			significant positive results, regardless of the ECG monitoring device used." This assumption cannot be changed in the *de novo* model.
With KardiaMobile, only patients receiving a positive result are followed-up with a visit to the GP or cardiologist. Otherwise, the clinician reaches a decision based on an interpretation of the ECG findings submitted.	Clinical expert opinion.	Clinical expert opinion	The EAC agrees with the assumption that only positive results would require an outpatient appointment (in line with EAC comment above).
The base case cost-effectiveness analysis considers ambulatory ECG in a secondary care setting.	Based on the NICE Scope document.	Clinical expert opinion	The EAC agrees that follow-up could be conducted in an outpatient setting (the EAC notes that the published clinical evidence had included the use of KardiaMobile in emergency departments, and inpatient and community settings).
The model consists of symptomatic patients only.	The asymptomatic population will not be included in the model due to the small proportion of the population who are candidates for ambulatory ECG, and the lack of data for the asymptomatic population regarding the probability of a positive test with KardiaMobile and other comparators in the ambulatory setting.	NICE Scope document	The EAC agrees with this assumption.
In the model, negative, and confirmed positive results by the clinician will not lead to repeat ambulatory ECG.	Clinical expert opinion.	Clinical expert opinion	The EAC agrees that a diagnosis of AF (or absence of AF) confirmed by clinical interpretation of the KardiaMobile ECG would not require repeated ECG monitoring.

Where monitoring is repeated (undiagnosed AF patients), the same device (always in the case of KardiaMobile) or an alternative technology may be used (for example,CER after Holter 24h) following the initial monitoring. The use of an implantable device is an option when there is a significant concern. The model assumes a maximum of two repeat tests, including implementable[sic] loop recorders (LRs), after the initial test.	Clinical expert opinion.	Clinical expert opinion	The EAC assumes that repeat testing with KardiaMobile is only used when the clinician deems the KardiaMobile ECG unreadable (however this is not clearly described in the Economic Submission). 24-hour Holter: first round of repeat monitoring includes 90% 7 day Holter, 10% CER, second round 70% CER, 30% implantable loop recorder [The EAC notes that this differs from the values stated in the company Economic Submission]. 48-hour Holter: first round of repeat monitoring includes 80% 7 day Holter, 20% CER, second round 70% CER, 30% implantable loop recorder [The EAC notes that this differs from the values stated in the company Economic Submission]. 7-day Holter: first round of repeat monitoring includes 60% 7 day Holter, 40% CER, second round 60% CER, 40% implantable loop recorder. 14-day Zio: first round of repeat monitoring includes 100% CER, second round 60% CER, 40% implantable loop recorder. [Note that the company has included CER and implantable cardiac monitor during repeat testing costings, however it is unclear why these were not considered as direct comparators in the first round of monitoring].

Table 17: Diagnostic yield of each device used in *de novo* model.

Device	Parameter	Value	Source	EAC comment
All	Prevalence of AF	30.43%	Sanna *et al.* 2014	Sanna *et al.* 2014 included patients aged 40 years or older (mean, SD age 61.5, 11.3 years), with stroke or TIA in previous 90 days and no history of AF or atrial flutter. The study reported poor follow-up beyond 24 months, but at 36 months follow-up the rate of detection of atrial fibrillation was 30% in the implantable cardiac monitor group (n=42 patients). The EAC was able to find prevalence of 30.0% and n=42 patients after 36 months of long-term follow-up, but note that the company model uses 42/138 to give 30.43% and the denominator could not be verified.
Holter (7d)	Diagnostic yield	14.80%	Hermans *et al.* 2021	Hermans *et al.* 2021 included patients aged 18 years or older (mean age 64.0 years) who had undergone ablation for paroxysmal AF. The study reported that 14.8% (17/115) of patients had AF detected by minimum 24-hour Holter monitoring (conducted at 3, 6 and 12 month follow-up). The *de novo* model assumed that 15.6% (AF prevalence 30.43%-14.8%) had undiagnosed AF missed by Holter monitoring. The EAC considers this an incorrect assumption because it combined values from unrelated studies.
Holter (48h)	Diagnostic yield	13.76%	Hermans *et al.* 2021	The *de novo* model assumed that 93.1% of 17 patients with AF detected in the Hermans study will have been detected within 48 hours (15.827 patients, 13.76%); 17 patients with AF detected is sourced from Hermans *et al.* 2021, however the source of 93.1% not provided. *De novo* model assumes that 16.67% (30.43% minus 13.76%) had undiagnosed AF missed by Holter monitoring. The EAC considers this an incorrect assumption because it combined values from unrelated studies.
Holter (24h)	Diagnostic yield	13.25%	Hermans *et al.* 2021	The *de novo* model assumed that 89.6% of 17 patients with AF detected in the Hermans study will have been detected within 24 hours (15.232 patients, 13.25%); 17 patients with

				AF detected is sourced from Hermans *et al.* 2021, however the source of 89.6% not provided. *De novo* model assumes that 17.18% (30.43% minus 13.25%) had undiagnosed AF missed by Holter monitoring. The EAC considers this an incorrect assumption because it combined values from unrelated studies.
Zio	Diagnostic yield	16.30%	Kaura *et al.* 2019	Kaura *et al*. 2019 included patients aged 18 years or older (mean age 70.7 years in patients receiving Zio patch monitoring) diagnosed with ischaemic non-lacunar stroke or TIA within previous 72 hours. The study reported that 16.3% (7/43) of patients had AF detected by Zio patch at 90 days. The *de novo* model assumed that 14.13% (AF prevalence 30.43% minus 16.3%) had undiagnosed AF missed by Zio monitoring. The EAC considers this an incorrect assumption because it combined values from unrelated studies.
CER	Diagnostic yield	16.07%	Gladstone *et al.* 2014	Gladstone *et al.* 2014 included patients aged 55 years or older, without known AF, with ischaemic stroke or TIA of undetermined cause within previous 6 months. The study reported that 16.07% (45/280) patients had AF detected by event-triggered recorder at 90 days. The *de novo* model assumed that 14.36% (30.43% minus 16.07%) had undiagnosed AF missed by CER. The EAC considers this an incorrect assumption because it combined values from unrelated studies.
Implantable cardiac monitor	Diagnostic yield	Not applied in model	N/A	It is unclear to the EAC why implantable cardiac monitor has been included with repeat monitoring, but that its ability to detect AF and inform subsequent management has been omitted from the model.
KardiaMobile+Clinician	Diagnostic yield	92.79%	Hermans *et al.* 2021	A total of 7,838 ECG recordings from 115 patients were captured in the Hermans *et al.* 2021 study; the company excluded 49 which were categorised as unreadable by the Kardia app. Of the remaining 7,789 ECG recordings, 9.9% were possible AF, 80.4% were normal, 9.7% were unclassified. Of the 774 ECG recordings that were deemed

				possible AF by KardiaMobile, only 592 were confirmed positive following clinical review; therefore KardiaMobile categorised 1.3074 (774/592) more ECG recordings as AF than the clinician. The company have applied this scaling factor (from ECG recordings) to determine the proportion of patients who would have been classed as AF if the Kardia app determination had been used only; 1.3074*(29/115) = 32.96%. This approach is inappropriate as repeated ECGs (mean of 68 per patient) are not independent. The company has then distributed the remaining patients (67.04%) to normal and unclassified groupings using the ECG proportions: 59.83% normal sinus, 7.21% unclassified. The company then combined the proportion of positive (possible AF, 32.96%) and negative (normal sinus, 59.83%) results to get an overall diagnostic yield of 92.79%. The EAC cannot explain why both positive and negative results contributed to the diagnostic yield of KardiaMobile but that only positive results contributed to the diagnostic yield of comparators. The EAC considers this approach fundamentally flawed and inconsistent across study arms. The EAC additionally notes that the base case model refers to 92.79% diagnostic yield, which is the calculated value for the "KardiaMobile only" scenario. Using the calculated values presented in the *de novo* model, the EAC assumes the company intended to apply a diagnostic yield of 99.5% for "KardiaMobile+Clinician" intervention but have failed to do so in the base case of the final model received.
Abbreviations: AF atrial fibrillation; EAC external assessment centre; ECG electrocardiogram; TIA transient ischaemic attack				

Economic model parameters

9.2.3 Clinical parameters and variables

The company reported the values for the clinical parameters and variables used in the model in Table 3 of the Economic Submission. A variety of sources were used, as summarised in Table 18.

The model contains over 150 parameters and the majority were described as "other parameters" in Table 4 of the Economic Submission. However, the EAC identified a number of discrepancies between the values described in Table 4 Economic Submission and the values implemented in the model, which the company confirmed were a consequence of complexity and updated iterations of the model (EAC Communication Log, 2021). The EAC does consider some of the remaining parameters (and their corresponding values) as inappropriate. For example, the company stated in their Economic Submission, major gastrointestinal bleed rates for AF patients of 1.15% for those taking aspirin, 1.11% for those taking warfarin, and 13.4% for those taking NOAC. 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. Two clinical experts disagreed with the company's rates of use for each medication, both stating that they do not use aspirin to treat AF at all (5% in the company's *de novo* model).

Similarly, the company applied a 0.51 hazard ratio of experiencing major gastrointestinal (GI) bleeding to the patients with undetected AF (that is those patients with AF who were not detected by a given device and thus prescribed no therapy) in the model. When queried by the EAC, the company clarified that: *"As undetected AF patients will not receive any medication, they are less likely to experience bleeding events than detected AF patients who will receive medication and are at a high risk of drug-related adverse events"* (EAC Communications Log, 2021). Using the SPARC tool for patients aged 65 year or less, the annual risk of major bleed with no therapy is 0.25% and 1.1% with aspirin (hazard ratio, HR 0.23), 2.4% with warfarin (HR 0.10), and 1.9% with Dabigatran 110mg twice daily (HR 0.13). Therefore the EAC considers the company value unlikely.

Additionally the company stated in the Economic Submission that the hazard ratios for adverse events (stroke, major GI bleed, MI or intracerebral haemorrhage ICH) for given medication regimes were primarily based on data from Hill *et al*. 2020. The EAC asked the company to clarify this further; the company responded with a screenshot of a supplementary table containing the values used in the model and directed the EAC to the supplementary material. Having checked this source, the EAC remained unable to verify the parameters.

Table 18: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value (distribution, if applied)	Source	EAC comment
Age	64 (62 to 66) years	Hermans *et al.* 2021	Median age from Hermans *et al.* 2021 applied. Age is used to determine risk of death in cohort at each cycle in the *de novo* model. The hazard ratio of major bleed with no treatment (via the SPARC tool) and the risk of stroke (via the CHA_2DS_2-VASc score) both depend on age. However, age does not impact AF prevalence, or risk of stroke in the *de novo* model (EAC Communication Log 2021).
Male patients	55.27%	NHS Hospital Episodes Statistics 2019/20 data	The EAC has confirmed that this value has been derived from Hospital Episode Statistics (HES) Admitted Patient Care Activity (APC) 2019-2020. Primary Diagnosis 3 character I48 (Atrial fibrillation and flutter): 54.77% (89,978/164,255). Gender is used to determine risk of death in cohort at each cycle in the *de novo* model. Risk of stroke (via the CHA_2DS_2-VASc score) depends on gender, however gender does not impact AF prevalence, or risk of stroke in the *de novo* model (EAC Communication Log 2021).
Prevalence of AF	0.30 (0.23-0.38)	Sanna *et al.* 2014	Sanna *et al.* 2014 included patients aged 40 years or older, with stroke or TIA in previous 90 days and no history of AF or atrial flutter. The study reported poor follow-up beyond 24 months, but at 36 months follow-up the rate of detection of atrial fibrillation was 30% in the implantable cardiac monitor group (n=42 patients).

			The EAC considered that this prevalence (in a high-risk group, determined at 3 years) was not appropriate for a diagnosis model over 100 days. The EAC notes that KardiaMobile detection of AF in the clinical evidence varied by subgroup (Table 9): - Undiagnosed palpitations (2 studies); 6.5% to 18.2% - AF recurrence following treatment (3 studies); 25.2% to 60.9% - Post-stroke or TIA (2 studies); 8.8% to 9.5% One expert considered 30% prevalence to be possible in patients after stroke or TIA, but estimated prevalence of AF in patients with undiagnosed palpitations who had negative 12-lead ECG to be much lower, at around 6%. The EAC notes that the AF prevalence will change during repeat monitoring (fewer patients likely to have AF at second and third testing). However AF prevalence remained static in the model.
Duration of monitoring with KardiaMobile (days)	14	Hermans *et al.* 2021	Hermans *et al.* (2021) included 115 patients aged 18 years and older who had undergone ablation for paroxysmal AF. Patients were instructed to use KardiaMobile 3 times daily and when symptomatic for a period of 4 weeks to detect AF recurrence. The study states that all patients with confirmed AF recurrence were detected within 14 days, however KardiaMobile was provided to patients at either their 3, 6 or 12 month follow-up, therefore 14-day diagnosis time does not reflect this usage.

			A duration of 14-day monitoring may not apply directly to other subgroups mentioned in the EAC critique of the Clinical Submission (for example patients with undiagnosed palpitations, patients monitoring AF burden). The EAC notes that the majority of clinical evidence included long-term use of KardiaMobile (for example Javed *et al.* 2021 used up to median of 20 months). Four clinical experts stated that they have used KardiaMobile and reported duration of use varied between 14 and 90 days. No distribution in monitoring duration was applied in the model. Unreliable assumption.
Duration of monitoring with Zio (days)	14	NICE MTG52, 2020	MTG52 (2020) states that the Zio patch can be worn for up to 14 days. "Evidence from comparative studies suggested that most patients were happy to wear the Zio XT biosensor, with median wear time ranging from 10.8 days (Rosenberg *et al.* 2013) to 12.8 days (Eysenck *et al.* 2019) out of a scheduled 14 days." Note that the comparator in MTG52 was considered as 24-hour Holter monitoring. The EAC considers that 14 days represents an upper estimate.
Maximum duration of monitoring with CER (days)	30	Assumption	Continuous event recorder (CER) is not explicitly defined as a comparator in the company Economic Submission, but is included within comparator arm within repeat monitoring costs. Experts advised that the duration of CER routinely used in the NHS ranged from 7 to 30 days.
Waiting time for diagnosis with Zio, Holter, CER (days)	3 (2-5)	Kaura *et al.* 2019	Kaura *et al.* 2019 included patients aged 18 years or older with cryptogenic ischaemic stroke or TIA within past 72 hours, with no history of AF or atrial flutter. Patients were randomised to either standard care (Holter monitoring, approx. 24 hours) or patch based monitoring (Zio patch, 14 days). Primary outcome was detection of AF lasting at

			least 30 seconds within 90 days. This study does not report waiting time for diagnosis. Company confirmed incorrect reference was provided (EAC Communication Log, 2021). The company confirmed that wait time represents the time between finishing monitoring and the availability of results for clinical review (EAC Communication Log, 2021). The company also confirmed that MTG52 2020 includes 2 day wait time for the report of results being available following Zio patch monitoring. The company confirmed that an additional day to book an appointment for the patient was added. The EAC notes that Zio XT is a service (consisting of 14-day patch, analysis of ECG by the company, and the report generated for clinician review provided within 2 days of the company receiving the patch, as described in MTG52), and therefore considers the company estimate (and distribution) as unlikely for Zio, and not applicable to the other comparators.
Waiting time for diagnosis with KardiaMobile (days)	3 (2-5)	Assumption	The clinical experts summarise that the time between the patient emailing the KardiaMobile ECG and clinical review varies; within 1 working day, reviewed 3 times weekly, once weekly, or not emailed and instead reviewed at end of monitoring duration (between 14-90 days). The EAC considers the company estimate (and distribution) as highly unlikely to reflect practice in NHS.
Rate of repeat monitoring after Holter	0.27	NICE MTG52, 2020	From MTG52 (summarising the EAC changes to the model): “the proportion of patients having repeat Holter tests after 24-hour Holter monitoring was changed to 27%”.

			Technology costs can be multiplied by 1.27 to represent the cost implication of repeated monitoring, however there is a lack of clinical evidence to demonstrate the improved diagnostic yield of 24 hour and repeated 24 hour Holter monitoring when compared with KardiaMobile.
Rate of repeat monitoring after Zio	0.176	Calculation	In MTG52, the EAC estimated a mean of 1.465 additional tests were required for the group of patients requiring test repetition. The company has included 2.465 in their calculation to derive rate of repeat monitoring for Zio. The EAC queried this with the company and gained the following response: *"To estimate the proportion of patients who need test repetition, we have used a weighted average of one test for the proportion of patients who have AF and have been detected by Zio, and those who don't have AF. Moreover, 1+1.465 tests for those who have AF but are not detected in the initial test (i.e. 1-prevalece-AF+[sic]). In the case of Zio, the weighted average of number of monitoring would be 1.21. In the next step, we converted this value, considering two time of repeat monitoring (a quadratic equation). Therefore, we estimated a 17% chance of repeat monitoring in the case of Zio".* The EAC was unable to validate this calculation.
Rate of repeat monitoring after CER	0.179	Calculation	The company has taken the same approach as above to derive repeat monitoring rates for CER.
Rate of GP visits during the initial AF monitoring (base-case)	0.00	Clinical expert opinion	Set to 0 in company base case, and not included in any sensitivity analysis. It is unclear to the EAC why this has been included in the model.

Resource identification, measurement and valuation

The company reported the values for the cost parameters and variables used in the model in the Resource identification, measurement and valuation section of the Economic Submission. A variety of sources were used, as summarised in Table 19.

Table 19: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	EAC value	EAC comment
Cost of KardiaMobile (device)	£124.00	£82.50	The company confirmed that £82.50 represents the cost of KardiaMobile-1L device (VAT removed). The cost of KardiaMobile-6L was omitted from the model in error, costing £124.20 (excluding VAT) and was included in the final model update. The company also confirmed that the Kardia app is free of charge (EAC Communication Log, 2021). Feedback from clinical experts was that the KardiaMobile-1L is in wider use, and therefore the EAC considers the cost of £82.50 more appropriate.
Cost of Holter (24h, 48h, 7d)	£171.20	£176.42	MTG52, 2020 (based on NHS reference costs 2017/18): £168.12 The EAC inflated to 2020 using Office of National Statistics Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £176.42
Cost of Zio (14d)	£315.68	£265	The EAC notes that the company have used the incorrect device cost (Zio cost was updated to £265 during MTG52 guidance). MTG52, 2020 updated cost following consultation: £265 (no inflation applied).
Cost of CER	£171.20	£176.42	MTG52, 2020, Assumed same cost as Holter; £176.42
Cost of implantable loop recorder	£3280.01	£1574.97	The company used costs of £3221 from MTG52, 2020 (which used 2017/18 reference costs) and inflated. However the EAC would consider more recent sources as more appropriate. DG41, 2020 (which updates and replaced MIB141) includes 3

			devices (costs from 2018): BioMonitor (£1030), Confirm Rx (£1600), Reveal LINQ (£1800), and additional £24.17 cost of 10 minutes implantation time; average cost of £1500.84. The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £1574.97
Cost of NOACs (daily)	£1.91	£1.35	Company confirmed that cost was derived from TA607 "Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease" and inflated (EAC Communication Log, 2021). The company confirmed they included rivaroxaban 2.5mg and ticagrelor 60mg. Clinical experts advised that ticagrelor is not a NOAC, and that apixaban, dabigatran, edoxaban, rivaroxaban are the appropriate medications. One expert advised that NOAC choice would be guided by bleed risk, stroke risk, renal function and compliance. EAC calculated the average price of 4 NOACs from BNF: £1.35 per tablet).
Cost of Warfarin (daily)	£0.06	£0.06	BNF warfarin sodium 500mg tablets (Drug tariff price; £1.56 per pack of 28, £0.06 per tablet). Cost of regular appointments for monitoring were not included in the *de novo* model.
Cost of Aspirin (daily)	£0.04	£0.04	BNF aspirin 75mg tablets (Drug tariff price; £1.21 per pack of 28, £0.04 per tablet)
Cost of stroke (first year)	£9260	£9527.12	TA607 Ischaemic stroke (which used NHS Reference costs 2017/18): £9078.69 The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £9527.12
Cost of stroke (subsequent years)	£1954	£2192.73	Walker *et al.* 2016 Non-fatal ischaemic stroke (which used NHS costs 2011/12), £448 for subsequent 90-days, which would give £1816.89 per year.

			The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/93.3); £2192.73
Cost of major bleed (first year)	£763	£784.84	TA607 Major non-fatal extracranial bleed (which used NHS Reference costs 2017/18): £747.90 The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £784.84
Cost of major bleed (subsequent years)	£0	No recommendation by EAC	The costs of adverse events have been taken from TA607. The EAC assumes that if the cost of major bleeding in subsequent years was not included in TA607, then the proportion of patients having a major bleed in subsequent years should be 0% and not contribute to adverse event counters. The company model does not follow this logic.
Cost of intracranial haemorrhage (first year)	£15,251	£15,690.41	TA607 Intracranial haemorrhage (which used NHS Reference costs 2017/18): £14,951.87 The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £15,690.41
Cost of intracranial haemorrhage (subsequent years)	£2922	£3279.30	Walker *et al.* 2016 Non-fatal haemorrhagic stroke (which used NHS costs 2011/12), £670 for subsequent 90-days, which would give £2717.22 per year. The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/93.3); £3279.30
Cost of MI (first year)	£3736	£3843.32	TA607 (which used NHS Reference costs 2017/18): £3662.42. The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £3843.32
Cost of MI (subsequent years)	£2098	£2354	Walker *et al.* 2016 (which used NHS costs 2011/12), £481 for subsequent 90-days, which would give £1951 per year.

			The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/93.3); £2354
Cost of fatal event (stroke, major bleeding, ICH, MI)	£2258	£2499	Walker *et al.* 2016 (which used NHS costs 2011/12)); fatal CVD event £2071 The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/93.3); £2499
Cost of GP visit	£39	£33	Personal Social Services Research Unit PSSRU 2019/20 GP unit costs (including direct care, based on 9.22 minute surgery consultation); £33 However GP visits do not appear in the company base-case or in any sensitivity analysis, therefore could have been removed from the model.
Cost of cardiologist visit	£151	£154.43	NHS reference costs 2018/19 for consultant-led cardiology outpatient appointment (service code: 320); £151 The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/110.1); £154.43
Cost of nurse services (Band 6) per working hour	£47	£50	PSSRU 2019/20 Hospital-based nurse (Band 6); £50
Nurse time for preparation of KM and patient training	10 minutes	10 minutes	This contributes to KardiaMobile per use costs. Four clinical experts stated that this was a reasonable assumption. Three reported that 20 minutes were required with some patients, or if the Kardia app had not been downloaded or installed beforehand). Two experts also stated that they do not use nurses for this, with one expert stating that physiologists (band 5) are used and another expert stating that healthcare assistants are used.
Interval between monitoring episodes	5 days	No recommendation by EAC	This contributes to KardiaMobile per use costs. The EAC interprets this parameter to represent the time between patients. Assuming a 2-year life expectancy of the device, and 14 monitoring

			period with Kardiamobile and 5 day interval between patients, the company model assumes that each device will be used a total of 38 times ((2x365)/(14+5)). The EAC considered that 38 uses per device was unlikely when used in an NHS setting.

9.2.4 Sensitivity analysis

The company conducted one-way sensitivity analysis across a total of 41 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 50%, for cost parameters.

Probabilistic sensitivity analysis, across 1,000 simulations was also conducted in the company model to account for uncertainty in the parameter estimates, for the base case.

9.3 *Results from the economic modelling*

All results from the company *de novo* model were taken from the most recent model received (19/05/2021). The base case results (Table 9 of company Economic Submission) can only be obtained by selecting KardiaMobile followed by clinician review of ECG as the intervention in the executable model. This was not explicitly stated in the company Economic Submission.

9.3.1 Base case results

The company base-case reports the following costs, and cost savings over the 5-year duration, Table 20.

Table 20: Results from company base-case

	Total cost	Cost difference
KardiaMobile + Clinician	£2,941.19	
Holter (24-hour)	£3,262.69	-£321.50
Holter (48-hour)	£3,260.94	-£319.75
Holter (7 days)	£3,273.84	-£332.65

Zio patch (14 day)	£3,323.99	-£382.80

9.3.2 Sensitivity analysis results

The company report that all sensitivity analysis resulted in KardiaMobile being cost saving. In the company's one-way sensitivity analysis, comparing KardiaMobile with 24-hour Holter monitoring (including repeat monitoring with different devices), the variables with the largest impact on incremental cost were:

- probability of AF positive (KardiaMobile + Clinician),
- proportion of patients on NOAC, and
- probability of diagnostic yield (24-hour Holter).

The PSA included a total of 1,000 iterations, comparing KardiaMobile and clinical interpretation of the ECG against the following comparators over a 5 year time horizon. 100% of simulations comparing against Holter monitoring (24-hour, 48-hour and 7-day) and 99.9% of simulations comparing against Zio patch demonstrated KardiaMobile as cost-saving, Table 21. Due to significant overlap between cost-saving results of Holter comparator arms, the EAC considered that a single duration of Holter monitoring would have been appropriate.

Table 21: Results of PSA conducted using company *de novo* model.

Comparator	Cost difference ((KardiaMobile+Clinician) – Comparator), [95%CI]	Cost saving, %
Holter (24-hour)	-£325 [-£472 to -£138]	100.0
Holter (48-hour)	-£325 [-£475 to -£132]	100.0
Holter (7-day)	-£337 [-£485 to -£149]	100.0
Zio (14 day)	-£383 [-£538 to -£192]	99.9

9.3.3 Additional results

The EAC could not verify the company model. The EAC did not independently replicate it as it disagreed with the model structure, underlying assumptions, parameter choices and implementation. The EAC was able to re-run the executable model in order to obtain the same output as the Company base case (Economic Submission, Table 9). The EAC changed parameters of the company model to understand its implications, Table 22.

Table 22: EAC univariate changes to company model

Scenario	Cost difference (KardiaMobile – Holter, 24-hours)	Cost difference (KardiaMobile – Zio)	EAC comment
Company base-case	-£321.50	-£382.80	
Cost of KardiaMobile changed from £124 to £82.50	-£322.08	-£383.38	KardiaMobile-1L is in wider use. Reducing device price by £42 to technology price makes very little difference to total costs. This is because the model assumes the KardiaMobile device is used 38 times, and costs are limited to 100 day diagnostic phase (with only a small proportion requiring repeat monitoring). It is not possible to directly edit the number of device uses within the *de novo* model.
Intervention changed from KardiaMobile+Clinician, to KardiaMobile only	-£212.94	-£274.24	The device's instructions for use state that clinical review is required for diagnosis of AF, therefore the EAC agrees with the approach taken in the base case. However changing the scenario to include KardiaMobile only as the intervention incurs £110 in each arm. This is driven by more patients being given anticoagulants in the KardiaMobile only scenario (costs incurred for anticoagulants have doubled, as have the costs due to two, three, and four adverse events meaning reduction in cost saving). This is a consequence of model parameter choice: probability of true positive and true negative are both 100% for KardiaMobile, and 74.1% and 99.7% for KardiaMobile and Clinician. The EAC disagrees with this assumption.
Prevalence of AF changed from 30% to 10%	-£426.57	-£449.86	Reduction in prevalence reduces anticoagulant costs, and also reduces costs associated with adverse events.

Cost of implantable loop recorder changed from £3280 to £0	-£252.27	-£341.61	Limited impact due to only small number requiring repeated monitoring, and even smaller proportion requiring second repeat (which is when the costs of implantable loop recorders are included in the model).
Cost of Zio changed from £315.68 to £265	-£321.50	-£332.12	Reduction of Zio device costs results in expected reduction of per patient costs (£50.68).
Only initial monitoring comparison changed from 'No' to 'Yes' (excluding repeat monitoring)	-£97.74	-£283.45	Excluding repeated monitoring has a larger impact on the Holter comparator arm than Zio.
Set rate of repeat monitoring after Holter to 0%	-£90.23	-£382.80	No impact on Zio arm, as expected. However it is unclear why the cost saving is different to the scenario above which uses the built-in model functionality (when Initial monitoring comparison set to 'Yes').
Set rate of repeat monitoring after Zio to 0% (company provided instructions of how to do this using Inter-calculation worksheet, EAC Communication Log, 2021)	-£321.50	-£275.94	No impact on Holter arm, as expected. However it is unclear why the cost saving is different to the scenario above which uses the built-in model functionality (when Initial monitoring comparison set to 'Yes').
Increase nurse time from 10 to 20 minutes	-£313.52	-£374.83	Additional 10 minutes of nurse time increases KardiaMobile cost per use by £7.83; the overall increase in costs slightly higher due to repeated monitoring in a small proportion of patients.
Decrease duration of monitoring with CER from 30 days to 7 days	-£230.77	-£350.85	Changing duration of CER monitoring automatically changes rate of repeat monitoring after CER. The EAC is unclear why the two parameters are linked.
Include hospital visit changed from positive cases only to all cases (KardiaMobile only)	-£218.45	-£279.75	Savings drop as expected to account for the increase in hospital visit follow-up appointment.

Include hospital visit changed from positive cases only to all cases, and all repeat monitoring set to 0%	-£3.49	-£182.22	Larger impact on Holter comparator arm than in Zio.

9.4 *The EAC's interpretation of the economic evidence*

The EAC disagreed with the structure and underlying assumptions of the company's *de novo* economic model. The EAC felt that there was not robust evidence to justify the inclusion of time-dependent probabilities in the diagnostic phase of the model.

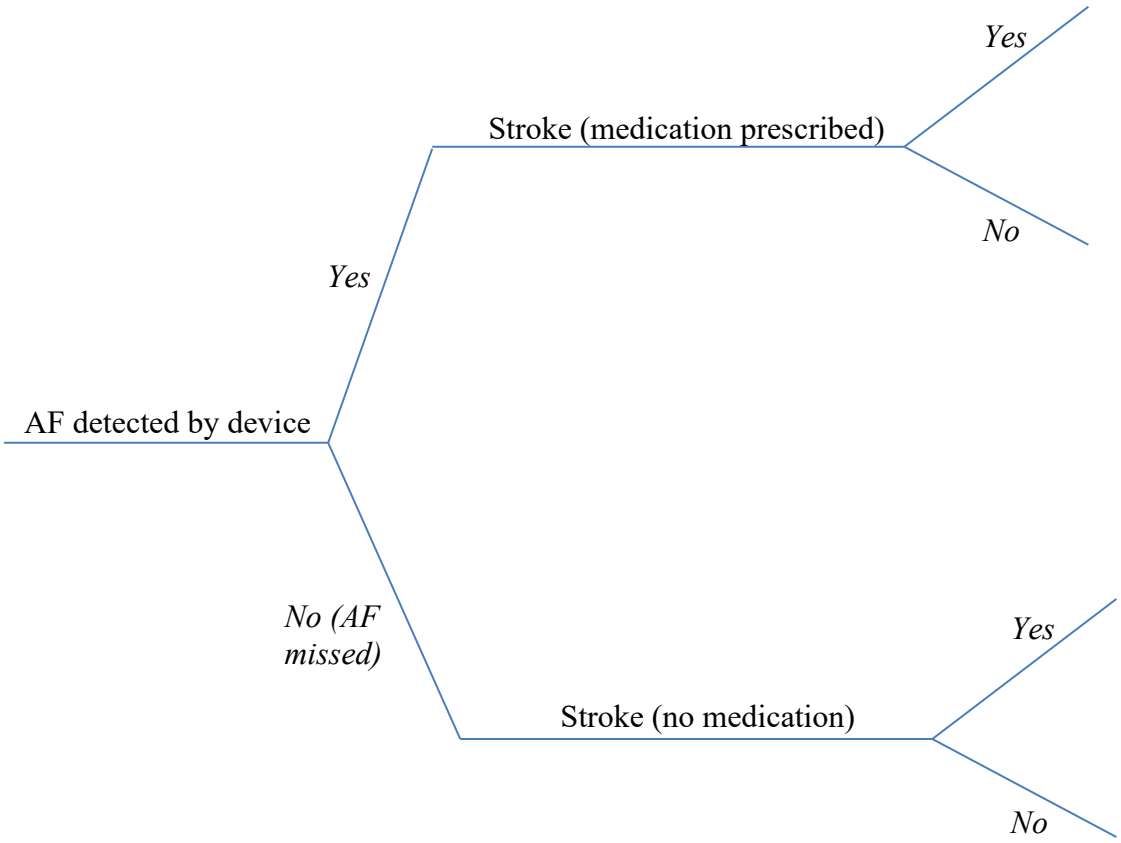
9.4.1 EAC cost calculator

The EAC created a simplified cost calculator to estimate the potential cost consequence of using KardiaMobile to detect AF, informed by results of comparative studies included in the clinical evidence. The EAC recognised a lack of diagnostic accuracy studies reporting on the sensitivity and specificity of AF detection on a *per-patient* basis. However, given that the device instructions for use recommend KardiaMobile ECGs are reviewed by a clinician, and that ESC 2020 Guidelines state that a single-lead ECG trace of 30 seconds or more can be used to diagnose AF, the EAC instead based the cost calculator on the increased diagnostic yield of KardiaMobile (in detecting more patients with AF than other devices). The general approach to the cost calculator is illustrated by a simple decision tree, Figure 3, with the following assumptions:

- 1 year-time horizon;
- Risk of stroke is determined from CHA_2DS_2-VASc score;
- Median CHA_2DS_2-VASc score of 2 in cohort (varied in sensitivity analysis up to maximum CHA_2DS_2-VASc score of 6);
- All CHA_2DS_2-VASc scores are given medication;
- All KardiaMobile ECGs are reviewed by a clinician, therefore it is assumed that KardiaMobile has 100% sensitivity and 100% specificity (therefore no cost impact of false negative or false positive results);
- ECG review time was considered broadly equal in both arms and therefore excluded from the analysis;
- The diagnostic yield from 6 comparative studies (included in the clinical submission) were applied to the cost calculator, each as a different scenario.

- Increased AF detection from 3 RCTs and 1 case-control study are an estimate as the data are not paired.

Figure 3: Structure of the EAC cost-calculator.



The parameters within the cost calculator are described in Table 23.

Table 23: Parameters used in the EAC cost calculator

Parameter	Value	Source
KardiaMobile (single lead version) device cost	£82.50	AliveCor. Feedback from experts was that the single lead device was more commonly used in the NHS.
No. of uses per KardiaMobile device	8	Assumption based on 2 year expected device life, and maximum of 90 days monitoring per patient (730/90=8 uses). This parameter will be varied in sensitivity analysis.
KardiaMobile training costs	£12.50	Based on 15 minutes of Band 6 nurse time (£50 per hour, PSSRU, 2019/20) based on feedback from clinical experts that 10

		minutes was appropriate for some patients but 20 required for others.
Holter monitoring costs	£176.42	MTG52 2020 (£168.12), inflated to 2020. Diagnostic yield of repeat Holter monitoring is not within the included clinical evidence, therefore not included in the EAC basecase.
Missed AF diagnoses	Varied by study	EAC will adopt the cost consequence analysis for all comparative studies which have reported on diagnostic yield (AF detection) between arms.
Risk of stroke in untreated AF	2.20%	Represents CHA_2DS_2-VASc score of 2. This will be varied in sensitivity analysis.
Risk reduction to stroke in treated AF	68%	Hobbs et al. (2005); risk reduction associated with warfarin.
Cost of anticoagulation (including cost associated with venous thromboembolism acute treatment)	£368.05	NG196, 2021 (Table 10) including average cost of warfarin and 4 NOACs: dabigatran, edoxaban, rivaroxaban, apixaban.
1-year health cost of stroke	£14,116.45	Xu et al. 2018; £13,452 mean healthcare costs in year 1 from SSNAP audit. Inflated to 2020 prices (112.6/107.3).
Abbreviations: AF atrial fibrillation; EAC external assessment centre; NOAC novel anticoagulant; SSNAP sentinel stroke national audit programme.		

The cost calculation for the scenario based on Hermans *et al*. (2021) which compared KardiaMobile to three rounds of (minimum 24-hour) Holter monitoring is described in Table 24.

Table 24: Cost consequence analysis using the scenario of Hermans *et al.* (2021).

	Intervention: KardiaMobile (n=115)	Comparator: Holter (n=115)
Number of patients	115	115
AF detected	29 (25.2%)	17 (14.8%)
AF missed	0	12 (10.4%)
Expected strokes (AF detected)	0.20	0.12
Expected strokes (AF missed)	0	0.26
Technology costs	£2,623	£60,865
AF treatment costs (incl. bleeding)	£10,673	£6,257
Stroke treatment costs	£2,882	£5,416
Total costs	**£16,179**	**£72,538**
Total costs, per patient	**£140.69**	**£630.76**

Cost difference, per patient (KardiaMobile – Comparator)	**-£490.08**

The EAC applied 6 scenarios, including data from six comparative studies which had different study sizes ranging between 33 and 240 patients, and where KardiaMobile detected additional proportion of patients with AF ranging between 6.1% and 30.4%. KardiaMobile was found to be cost saving versus the comparator (Holter or external loop recording) in 3 studies; cost savings ranged from £144 to £490 per patient, Table 25. One RCT (Reed *et al.* 2019) compared KardiaMobile in additional to standard care to standard care alone, and demonstrated a minimal cost expenditure of £32 per patient. The EAC considers that this scenario represents the cost of the KardiaMobile when used as an adjuvant diagnostic (that is as an additional test used alongside Holter monitoring). The remaining two studies (Goldenthal *et al.* 2019 and Hickey *et al.* 2017) both measured AF recurrence following treatment, and did not define "standard care", thus zero device costs were included for the comparator arm. Therefore the per-patient cost of surveillance in the comparator arm would have to exceed £41 and £71, for the Goldenthal and Hickey scenarios, in order for KardiaMobile to be cost saving.

Table 25: Cost consequence analysis across six comparative studies.

Study	Population	Comparator	AF detection (Intervention)	AF detection (Comparator)	Difference in AF detection (Intervention – Comparator)	Intervention cost (per patient)	Comparator cost (per patient)	Cost difference (Int-Comp)
Hermans *et al.* 2021 Netherlands (n=115)	AF recurrence	3 rounds of min. 24-hour Holter	25.2%	14.8%	10.4%	£140.69	£630.76	-£490.08
Narasimha *et al.* 2018 US (n=33)	Palpitations	External loop recorder	18.2%	12.1%	6.1%	£107.80	£251.90	-£144.10
Koh *et al.* 2021 Malaysia (n=203)	Stroke/TIA	Additional round 24-hour Holter	9.5%	2.0%	7.5%	£67.33	£211.31	-£143.98
Reed *et al.* 2019 UK (n=240)	Palpitations	Standard care	6.5%	0%	6.5%	£52.97	£21.42	£31.55
Goldenthal *et al.* 2019 US (n=233)	AF recurrence	Standard care (undefined)	50.4%	41.5%	8.9%	£258.56	£217.79 (unknown device costs)	£40.77
Hickey *et al.* 2017 US (n=46)	AF recurrence	Standard care (no ECG monitoring; undefined)	60.9%	30.4%	30.4%	£307.33	£236.78 (unknown device costs)	£70.55
Abbreviations: AF atrial fibrillation; ECG electrocardiogram; TIA transient ischaemic attack								

9.4.2 Cost calculator sensitivity analysis

The cost impact of varying CHA_2DS_2-VASc score (which varies the risk of stroke) are described in Table 26. Cost savings increased with CHA_2DS_2-VASc score. All studies became cost saving when a score of 6 was used (risk of stroke 9.8%).

Table 26: Cost impact of varying CHA_2DS_2-VASc

	Cost difference (Intervention-Comparator) by CHA_2DS_2-VASc					
Study	1‡	2*	3	4	5	6
Hermans *et al.* 2021 Netherlands (n=115)	-£481.06	-£490.08	-£500.10	-£508.11	-£535.15	-£566.20
Narasimha *et al.* 2018 US (n=33)	-£138.86	-£144.10	-£149.92	-£154.57	-£170.28	-£188.31
Koh *et al.* 2021 Malaysia (n=203)	-£136.65	-£143.98	-£152.13	-£158.64	-£180.63	-£205.87
Reed *et al.* 2019 UK (n=240)	£37.69	£31.55	£24.73	£19.27	£0.86	-£20.29
Goldenthal *et al.* 2019 US (n=233)†	£46.84	£40.77	£34.03	£28.63	£10.43	-£10.47
Hickey *et al.* 2017 US (n=46)†	£96.85	£70.55	£41.34	£17.97	-£60.91	-£151.48
**Basecase* *†Device costs not included in comparator arm (not defined)* *‡ Assumes medication is prescribed (NG196 implies this is valid for male patients only).*						

The cost impact of varying the number of times KardiaMobile device is used is described in Table 27, the direction of cost saving and cost incurring remains unchanged even when KardiaMobile is used 104 times (average of 7 days per patient).

Table 27: Cost impact of varying number of KardiaMobile device uses.

	Cost difference (Int-Comp) by number of KardiaMobile device uses				
Study	8* (90 days)	16 (45 days)	24 (30 days)	52 (14 days)	104 (7 days)
Hermans *et al.* 2021 Netherlands (n=115)	-£490.08	-£495.23	-£496.95	-£498.80	-£499.60
Narasimha *et al.* 2018 US (n=33)	-£144.10	-£149.26	-£150.98	-£152.83	-£153.62
Koh *et al.* 2021 Malaysia (n=203)	-£143.98	-£149.14	-£150.86	-£152.71	-£153.50
Reed *et al.* 2019 UK (n=240)	£31.55	£26.39	£24.68	£22.83	£22.03
Goldenthal *et al.* 2019 US (n=233) †	£40.77	£35.61	£33.90	£32.04	£31.25
Hickey *et al.* 2017 US (n=46) †	£70.55	£65.40	£63.68	£61.83	£61.04
**Basecase* *†Device costs not included in comparator arm (not defined)*					

The cost calculator retains the main costs of the technology, treatment of AF, costs of bleeding consequential to treatment, and subsequent strokes. The parameter values, their sources, and how they are used in the calculator are transparent, and the number of uses for each KardiaMobile device has been assumed to be 8, which has been varied in sensitivity/scenario analysis to determine impact on total costs. Although the cost calculator could only be applied to results from a small number of studies (which were comparative in design and reported on diagnostic yield), the AF recurrence after treatment, and palpitations subgroups are reasonably well represented. However, there are limitations in this approach. The cost calculator did not consider risk reduction due to NOACs. The cost calculator provides no means of selecting a comparator; it is bound by the comparator chosen by each study – which varied for each. The consequence of this is that for two studies where the comparator arm was not explicitly defined (Goldenthal *et al.* 2019, Hickey *et al.* 2017) the EAC could not include a comparator device cost, and instead could only state the threshold comparator device cost at which KardiaMobile would become cost saving. This approach makes it less comprehensive than a *de novo* model, however given that diagnostic yield is study specific (depending on the frequency and duration of use of intervention and comparator), the EAC felt that this was the most appropriate.

Only one of the six studies included in the cost calculator was conducted in the UK, which may limit how generalisable the overall results are to use in the NHS. When the RCT by Reed *et al.* 2019, was included as a scenario, the cost calculator found KardiaMobile to be cost incurring. However the small cost increase (£31 per patient per year) can be considered the pathway cost of implementing KardiaMobile as an adjuvant diagnostic (alongside Holter monitoring). Due to the small numbers of patients in each study, the expected number of strokes avoided is not a whole number, but the EAC considered this more robust than introducing rounding error.

The EAC has examined the claimed benefits of KardiaMobile made by the company in the context of the economic evidence included, Table 28.

Table 28: *Summary of economic evidence for claimed benefits*

	Claimed benefits	Company supporting evidence	EAC opinion
Cost benefits	Reduction in costs and resource use	5 studies (2 excluded by EAC)	<u>Benefit likely</u> Published economic evidence demonstrates likely to be saving. The company *de novo* model demonstrates likely cost saving; however deemed unreliable by EAC due to structure introducing uncertainty and model assumptions not being valid or generalisable to NHS practice. The cost calculator developed by the EAC, applied to the published comparative studies included in the Clinical Submission, demonstrates likely cost saving due to reduction of strokes alone. May need to consider cost of phone or tablet when prescribing to patients. Added benefits: - Detection of other symptomatic rhythms: out of scope of this assessment but wider benefits to patient and NHS. - Technology enables remote care of patients: particularly of benefit in current pandemic. - Potential use of device in patient triage (after 12-lead ECG but before Holter monitoring); again may be of particular benefit during pandemic.

Sustainability benefits	Preventing cardiovascular disease leads to a reduction in hospital visits and resources, travel costs leading to CO_2 reduction.	No evidence provided.	Benefit likely Remote review of ECG recordings and feedback to patient would result in fewer hospital visits.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The company identified a total of 33 studies from their literature search. The EAC considered 15 of these as out of scope (reporting on populations, interventions and outcomes not included in the decision problem). The EAC identified an additional 14 papers from an independent search, including 2 published updates replacing studies submitted by the company. A total of 32 studies were included in the clinical evidence review: 7 RCTs, 7 diagnostic accuracy studies, 1 case-control, 16 single-arm observational studies, and 1 case report; however 14 were available in abstract form only.

The studies were heterogeneous in nature, conducted in different subgroups of patients (with different underlying prevalence of AF), in different settings, with KardiaMobile used at different frequencies and durations and compared with different reference standards. However, the heterogeneity in evidence reflects the range of uses of the KardiaMobile device in clinical practice. Four studies compared the Kardia Mobile's ECG rhythm classification with clinical interpretation as the reference standard: for AF detection sensitivity ranged from 92 to 99%, specificity ranged from 92 to 98%. Six comparative studies reported that KardiaMobile detected AF more frequently than 'standard care'; however standard of care varied across studies. Two RCTs confirm that KardiaMobile reduced the time to AF detection – however reduction in time to treatment and impact on subsequent strokes has not been quantified in the available evidence. The proportion of ECG recordings deemed unreadable by the automated detection software was low (<2%). The proportion of ECG recordings unclassified by the software ranged between 9.6% and 27.6% but has decreased over time, in line with software updates. However, clinical review can resolve many "unreadable" and "unclassified" KardiaMobile ECGs. The large volume of real-world observational data supports its ease of use. Two RCTs have additionally demonstrated improvements in Atrial Fibrillation Effect on Quality-of-Life (AFEQT).

10.2 *Conclusions from the economic evidence*

The company identified 5 published economic studies. The EAC considered 2 of these as out of scope (one included a screening population, and one was available only in abstract form and did not include any cost analysis). The remaining three studies (two set in the UK) demonstrated Kardia Mobile to be cost saving, largely through the reduction in healthcare appointments (emergency care, GP, ECG referral). The company provided a *de novo* Markov model consisting of more than 150 parameters, written in Microsoft Excel. The model consisted of two phases: diagnosis (maximum 100 days) and management (5 years). Two updates of the model were received. The company base-case scenario reported that the per-patient pathway costs over 5 years associated with using KardiaMobile were £2941, and was cost-saving by £322, £320, £333 and £383 per person when compared with pathway costs for 24 hour, 48 hour, and 7 day Holter, and 14 day Zio patch monitoring respectively. The EAC considered the model as overly complex, not transparent and not verifiable. The EAC did not agree with underlying structural assumptions, parameter choice or implementation in the *de novo* model.

With a simple cost-calculator informed by 6 comparative studies from the clinical evidence, the EAC estimated KardiaMobile to be cost-saving in 3 studies (ranging between £144 and £490 per patient) when compared with Holter or external loop recorder monitoring. The potential savings are driven by the increased rate of detection of AF with KardiaMobile, resulting in avoidance of strokes. When the single RCT conducted in the UK was included as a scenario in the cost calculator, KardiaMobile was cost incurring of £31 per patient. However the EAC considers that this scenario represents KardiaMobile being used as an adjuvant diagnostic alongside standard care. Two additional studies did not provide enough information to determine comparator arm costs, however the cost calculator identified the cost of comparator device which would result in KardiaMobile being cost saving.

Despite the limitations of the company model, the EAC considers it is plausible that KardiaMobile could be cost saving. However, the absence of a verifiable and transparent model that permits probabilistic sensitivity analysis

means that there remains uncertainty over the magnitude and confidence interval of cost savings.

11 Summary of the combined clinical and economic sections

The published clinical evidence for KardiaMobile consisted of 32 studies including a total of 2,801 unique patients, and a range of study designs (7 RCTs, 7 diagnostic accuracy studies, 1 case-control study, 16 single-arm observational studies, and 1 case report). The studies varied in quality and 14/32 (44%) were available in abstract form only. The studies demonstrated the use of KardiaMobile in 6 subgroups of patients with different underlying prevalence of AF, indifferent healthcare settings, and had a range of different reference standards. The heterogeneity of published evidence reflects the variation in clinical practice, and demonstrates the versatility of KardiaMobile to be used in different contexts to detect AF. There was consistent evidence that KardiaMobile detected more AF than other monitoring devices, and that KardiaMobile was easy to use.

The published economic evidence for KardiaMobile consisted of 2 peer-reviewed publications and one grey literature report; all of which demonstrated a cost-saving with KardiaMobile due to a reduction in healthcare appointments. The company *de novo* model also demonstrated KardiaMobile to be cost saving, however the EAC deemed the model results as unverifiable. A simple cost calculator created by the EAC demonstrated potential cost-savings across 3 comparative studies from the clinical evidence. This was through increased detection of AF and reduction of subsequent strokes with consequential reduction in costs of care. The absence of a verifiable model means that there remains uncertainty over the magnitude and confidence interval of savings for different scenarios.

12 Implications for research

Published evidence demonstrates increased AF detection and ease of use across a number of patient subgroups. Despite five randomised controlled

trials using KardiaMobile, there is a lack of direct evidence to demonstrate that use of KardiaMobile reduces time to treatment and subsequent strokes. However, given low prevalence of AF, low incidence of strokes, and the high sensitivity and specificity of devices being compared, the number of patients and length of follow-up required to demonstrate this benefit would be large. Further research in this area is unlikely to reflect the large variation in NHS practice and heterogeneity in patient subgroups using KardiaMobile. Therefore, the EAC does not consider the clinical uncertainties large enough to warrant further clinical trials with KardiaMobile.

The largest uncertainty remaining is the magnitude and confidence interval of cost-saving if KardiaMobile was implemented across the NHS. This could be addressed in a simplified model, developing upon the cost calculator created by the EAC, or those developed for previous technology assessments of AF diagnostic devices, and including probabilistic sensitivity analysis to assess the impact of varying diagnostic yield, uncertainty in costs of AF management and risk of stroke.

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14 Appendices

Use the appendices to describe additional data and information as needed – we've given some examples as a guide.

List the titles of the appendices here.

Appendix A: Clinical literature search

Appendix B: Critical appraisal of clinical evidence

Appendix C: Adverse events

Appendix D: Ongoing studies

Appendix E: Economic literature search

Appendix F: Critical appraisal of economic evidence

Appendix A: Clinical literature search

Appendix A1: PRESS checklist for search strategy peer review

Search Strategy (PubMed)	Database: PUBMED (All fields) <To February 05, 2021>		Result
	#1	(((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR (non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)	88,552 results
	#2	(((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro)	**19,879 results**
	#1 AND #2	(((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR (non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium	584

		fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)) AND ((((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro))	
Databases searched	• PubMed • Embase • Cochrane • ICTRP • ClinicalTrials.gov • Web of science		

Question	Y/N	Notes
Translation of the research question		
Does the search strategy match the research question/PICO?	Yes	
Are the search concepts clear?	Yes	Atrial fibrillation and Kardia
Are there too many or too few PICO elements included?	Okay	
Are the search concepts too narrow or too broad?	Too narrow	1) Some terms like 'mobile monitoring' (without additional qualifying terms, as a direct alternative for Kardia) – a bit broad. 2) Other terms used to search for results without a product-specific term could have been broadened, for example 'portable single lead ecg recorder' (or even just 'single lead ecg') wouldn't cover 'single lead echocardiogram'.
Does the search retrieve too many or too few records? (Please show number of hits per line.)	Okay	See above – the two effects mostly cancel out, in overall numbers (though some relevant material may have been missed).
Are unconventional or complex strategies explained?	N/A	
Boolean and proximity operators (these vary based on search service)		
Are Boolean or proximity operators used correctly?	Yes	However, significant redundancy in some of the searches, for example 'single lead ecg' OR 'portable single

		lead ecg' OR 'single lead ecg recorder' OR 'portable single lead ecg recorder' would be covered by just ‘single lead ecg’. Likewise, many of the atrial fibrillation terms.
Is the use of nesting with brackets appropriate and effective for the search?	Yes	Mostly fine. Somewhat excessive quantity of unnecessary brackets in PubMed, but largely a by-product of search interface; it doesn’t seem to break the logic of search.
If NOT is used, is this likely to result in any unintended exclusions?	N/A	
Could precision be improved by using proximity operators (eg, adjacent, near, within) or phrase searching instead of AND?	No	Proximity operators could not have been used in place of AND (nor could additional phrase searching). However, in the new version of the search, I did introduce proximity operators to broaden some elements of the search to cover a wider range of phrases.
Is the width of proximity operators suitable (eg, might adj5 pick up more variants than adj2)?	N/A	
Subject headings (database specific)		
Are the subject headings relevant?	Yes	Mostly, yes, except ‘Kardia/’ in Embase seems like it matches to ‘acetyldigoxin’ (as well as small number of results with ‘Kardia/’ candidate subject term). (Caveat: I tested this on Ovid, the original searches seem to have been run on a different platform)
Are any relevant subject headings missing; for example, previous index terms?	No	MeSH terms have not been used in PubMed but the ‘all fields’ searches should still retrieve those results.
Are any subject headings too broad or too narrow?	No	
Are subject headings exploded where necessary and vice versa?	No	The Embase product-specific subject terms (for example Kardia/, Kardiamobile/) have been exploded but don’t require exploding – they seem to be candidate terms and cannot be exploded; furthermore, exploding may mean the searches didn’t even function to return results with those individual candidate terms at all.
Are major headings (“starring” or restrict to focus) used? If so, is there adequate justification?	N/A	
Are subheadings missing?	No	

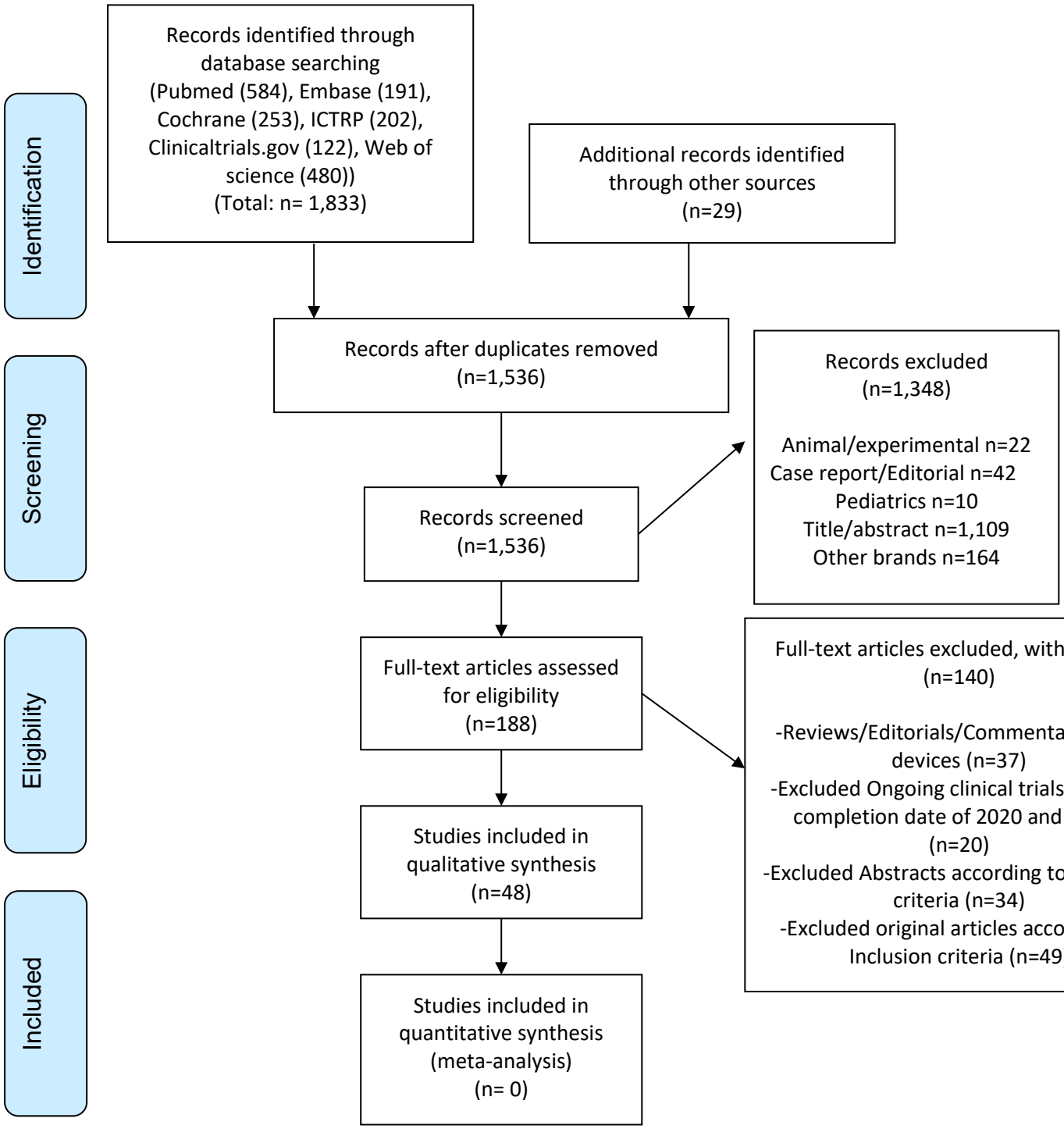
Are subheadings attached to subject headings? (Floating subheadings may be preferred.)	No	
Are floating subheadings relevant and used appropriately?	N/A	
Are both subject headings and terms in free text (see the following) used for each concept?	No	In the case of the 'Kardia' terms in Embase, they only seem to have been searched as subjects - even if the use of explode didn't prevent those candidate subject terms being searched (see comment above), the searches wouldn't have picked up on 'Kardia', 'Kardiamobile', etc in title/abstract.
Text word searching (free text)		
Does the search include all spelling variants in free text (eg, UK vs. US spelling)?	No	'Fibrillation'/'fibrilation' variations not always searched consistently
Does the search include all synonyms or antonyms (eg, opposites)?	Yes	Mostly yes, though there was still some scope for some additional synonyms.
Does the search capture relevant truncation (ie, is truncation at the correct place)?	N/A	Not used. If it had been used, it could perhaps have simplified some of the term combinations.
Is the truncation too broad or too narrow?	N/A	
Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?	N/A	
Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?	No	See prior comment. Some of the non-product-specific terms needed to be more specific (or qualified in some way), but that area also could have been covered by a broader range of alternative terms.
Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded (database specific)?	Yes	
Should any long strings be broken into several shorter search statements?	No	
Spelling, syntax, and line numbers		
Are there any spelling errors?	No	
Are there any errors in system syntax; for example, the use of	No	

a truncation symbol from a different search interface?		
Are there incorrect line combinations or orphan lines (ie, lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?	No	
Limits and filters		
Are all limits and filters used appropriately and are they relevant given the research question?	N/A	
Are all limits and filters used appropriately and are they relevant for the database?	N/A	
Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too narrow? Can any limits or filters be added or taken away?	N/A	
Are sources cited for the filters used?	N/A	

Further comments:

Changes made to the searches (depending on the search platform) included:
• Removing unnecessary duplicated terms
• Covering a slightly broader range of both product-specific terms and atrial fibrillation terms
• Adding nuanced combinations of terms to pick up more relevant (and less non-relevant) results without product-specific terms. These combinations were:
  ○ Any ECG term or subject + any smart or phone term or subject + single or six lead term
  ○ A diagnostic accuracy or device comparison subject/term + a smartphone or app subject
  ○ A specific smartphone/device term in proximity to any ECG term

Company's PRISMA diagram of literature search and sift for clinical evidence [Appendix A of company Clinical Submission]. EAC notes that the reasons for exclusion in the first exclusion box add up to 1347 and not 1348 as stated.



Appendix A2: Literature search conducted by EAC

Embase <1974 to 2021 April 09>

1	exp atrial fibrillation/	82013
2	((atri$ adj10 fibril$) or (auric* adj10 fibril*)).mp.	182714
3	1 or 2	182714
4	(kardia or kardiatm$ or kardiamobile$ or kardiaapp$ or kardiapro$ or alivecor$ or alive$ cor or alive cortm or aliveecg$ or alive$ ecg).af.	848
5	(ecg? or ekg? or electrocardiog$).mp.	327160
6	exp electrocardiograph/	17400
7	exp electrocardiography/	160178
8	exp electrocardiogram/	203185
9	5 or 6 or 7 or 8	390402
10	mobile phone/ or smartphone/	33424
11	mobile application/ or mobile health application/	15144
12	(smart$ or phone? or ehealth or e-health or mhealth or m-health or mobile health or pocket or portable).mp.	224315
13	((home? or mobile or ambulatory) adj5 monitor$).mp. or self monitoring/	49897
14	10 or 11 or 12 or 13	274848
15	(single lead or six lead$ or "6 lead$").mp.	2683
16	diagnostic accuracy/ or diagnostic test accuracy study/ or "electrocardiograph"/dc	363947
17	15 and 14 and 9	276
18	16 and (10 or 11) and 9	139
19	((smartphone? or ipad? or iphone?) adj6 (ecg? or ekg? or electrocardiog$)).mp.	303
20	17 or 18 or 19	583
21	limit 20 to conference abstract	211
22	20 not 21	372
23	3 and (4 or 22)	347
24	limit 23 to human	341
25	limit 24 to english language	337

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to April 09, 2021>

1	Atrial Fibrillation/	58386
2	((atri$ adj10 fibril$) or (auric$ adj10 fibril$)).mp.	89067

3	1 or 2	89067
4	(kardia or kardiatm$ or kardiamobile$ or kardiaapp$ or kardiapro$ or alivecor$ or alive$ cor or alive cortm or aliveecg$ or alive$ ecg).af.	599
5	(ecg? or ekg? or electrocardiog$).mp.	257004
6	exp Electrocardiography/	206998
7	5 or 6	261108
8	cell phone/ or smartphone/	14406
9	Mobile Applications/	7373
10	(smart$ or phone? or ehealth or e-health or mhealth or m-health or mobile health or pocket or portable).mp.	171557
11	(((home? or mobile or ambulatory) adj5 monitor$) or self monitor$).mp.	45747
12	8 or 9 or 10 or 11	215281
13	(single lead or six lead$ or "6 lead$").mp.	1825
14	((diagnos$ adj4 accura$) or ((evaluat$ or compar$) adj5 device?)).mp.	127011
15	(single lead or six lead$ or "6 lead$").mp.	1825
16	13 and 7 and 12	157
17	14 and 7 and (8 or 9)	36
18	((smartphone? or ipad? or iphone?) adj6 (ecg? or ekg? or electrocardiog$)).mp.	147
19	16 or 17 or 18	282
20	4 or 19	828
21	3 and 20	154
22	21 not (exp animals/ not humans.sh.)	154
23	limit 22 to english language	151

Cochrane Library (CENTRAL and CDSR). Date Run: 12/04/2021

ID	Search	Hits
#1	MeSH descriptor: [Atrial Fibrillation] this term only	4753
#2	(((atri* NEAR/10 fibril*) or (auric* NEAR/10 fibril*))):ti,ab,kw (Word variations have been searched)	13397
#3	#1 OR #2	13397
#4	((kardia or kardiatm* or kardiamobile* or kardiaapp* or kardiapro* or alivecor* or "alive* cor" or "alive cortm" or aliveecg* or "alive* ecg")) (Word variations have been searched)	61
#5	(ecg? or ekg? or electrocardiog*):ti,ab,kw	30473
#6	MeSH descriptor: [Electrocardiography] explode all trees	8849
#7	#5 OR #6	30579

#8	MeSH descriptor: [Smartphone] this term only	453
#9	MeSH descriptor: [Cell Phone] this term only	706
#10	MeSH descriptor: [Mobile Applications] this term only	748
#11	(smart* or phone? or ehealth or e-health or mhealth or m-health or "mobile health" or pocket or portable):ti,ab,kw	29340
#12	(((home? or mobile or ambulatory) NEAR/5 monitor*) OR (self NEXT monitor*)):ti,ab,kw	11023
#13	#8 OR #9 OR #10 OR #11 OR #12	39095
#14	("single lead" or "six lead*" or "6 lead*"):ti,ab,kw	145
#15	(diagno* NEAR/4 accura*) OR ((compar* OR evaluat*) NEAR/5 device?):ti,ab,kw	14589
#16	#7 AND #13 AND #14	31
#17	#7 AND (#8 OR #9 OR #10) AND #15	2
#18	((smartphone? or ipad? or iphone?) NEAR/6 (ecg? or ekg? or electrocardiog*)):ti,ab,kw	36
#19	#16 OR #17 OR #18	63
#20	#4 or #19	107
#21	#3 and #20	69
#22	MeSH descriptor: [Animals] explode all trees	601438
#23	MeSH descriptor: [Humans] explode all trees	601378
#24	#21 not (#22 not #23)	69

CENTRAL: 69 results

CDSR: 0 results

CINAHL (EBSCO)

#	Query	Results
S1	(MH "Atrial Fibrillation")	25,985
S2	((atri* N10 fibril*) or (auric* N10 fibril*))	35,921
S3	S1 OR S2	35,921
S4	TX (kardia or kardiatm* or kardiamobile* or kardiaapp* or kardiapro* or alivecor* or "alive* cor" or "alive cortm" or aliveecg* or "alive* ecg")	143
S5	ecg# or ekg# or electrocardiog*	55,352
S6	(MH "Electrocardiography+")	46,652

S7	S5 OR S6	57,551
S8	(MH "Cellular Phone") OR (MH "Smartphone")	5,006
S9	(MH "Mobile Applications")	8,719
S10	smart* or phone# or ehealth or e-health or mhealth or m-health or "mobile health" or pocket or portable	87,771
S11	(home# or mobile or ambulatory) N5 monitor*	8,606
S12	S8 OR S9 OR S10 OR S11	100,186
S13	"single lead" or "six lead*" or "6 lead*"	464
S14	(diagno* N4 accura*) OR ((compar* OR evaluat*) N5 device#)	34,623
S15	S7 AND S12 AND S13	58
S16	S7 AND (S8 OR S9) AND S14	10
S17	(smartphone# or ipad# or iphone#) N6 (ecg# or ekg# or electrocardiog*)	149
S18	S15 OR S16 OR S17	186
S19	S4 OR S18	299
S20	S3 AND S19	93
S21	(MH "Animals+")	94,988
S22	(MH "Human")	2,332,351
S23	S20 NOT (S21 NOT S22)	93
S24	Narrow by Language: - english	92

Clinicaltrials.gov

(kardia OR kardiatm OR kardiamobile OR kardiamobiletm OR kardiaapp OR kardiapptm OR kardiapro OR kardiaprotm OR alivecor OR alivecortm OR "alive cor" OR aliveecg OR "alive ecg") AND (atrial OR atrium OR auricular OR fibrillation OR fibrilation)

Link

38 results

EU Clinical Trials Register

(kardia OR kardiatm OR kardiamobile OR kardiamobiletm OR kardiaapp OR kardiapptm OR kardiapro OR kardiaprotm OR alivecor OR alivecortm OR "alive cor" OR aliveecg OR "alive ecg") AND (atrial OR atrium OR auricular OR fibrillation OR fibrilation)

Link

0 results

IDEAS/RePEc

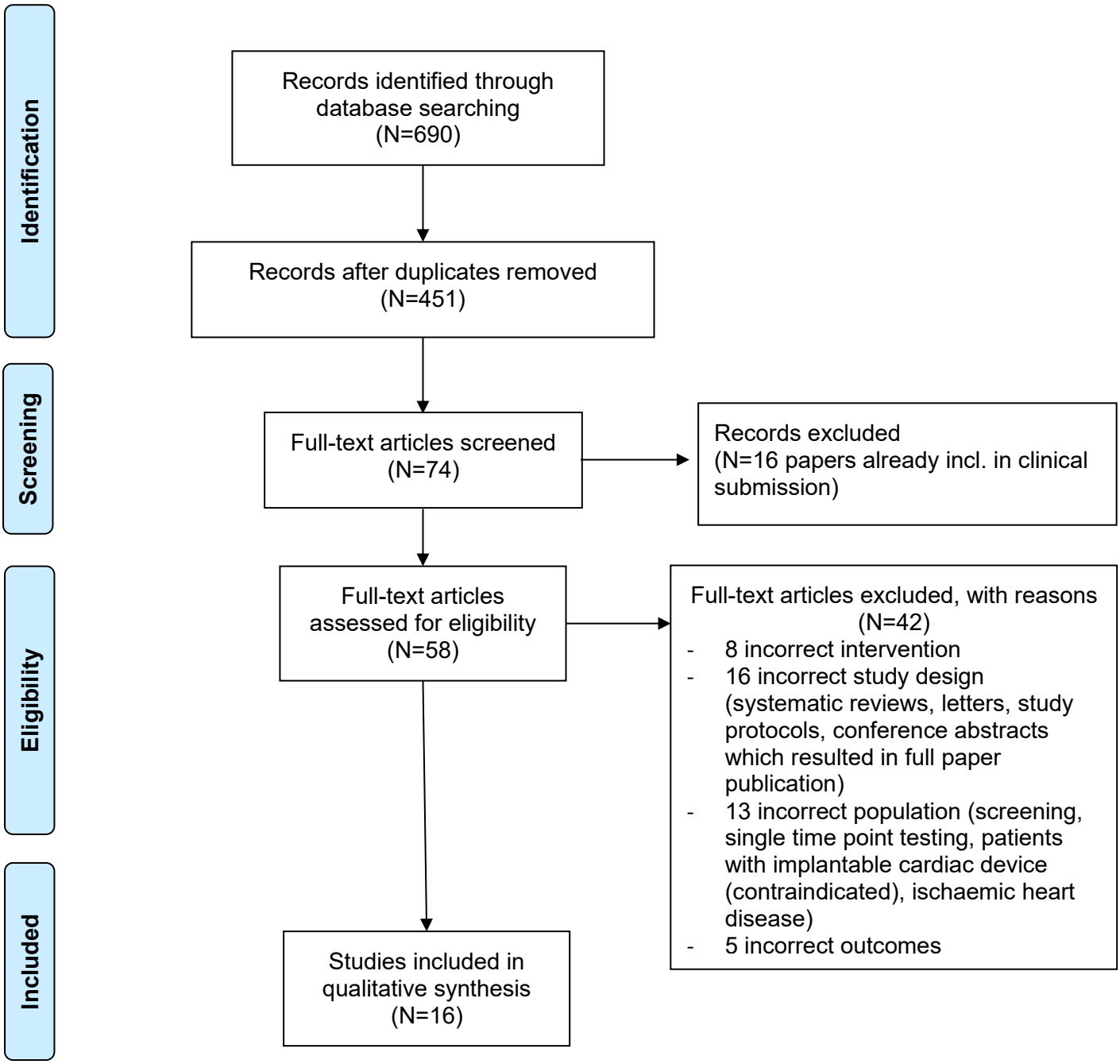
((kardia | kardiatm | kardiamobile | kardiamobiletm | kardiaapp | kardiapptm | kardiapro | kardiaprotm | alivecor | alivecortm | "alive cor" | "alive cortm" | aliveecg | "alive ecg") +(atrial | atrium | auricular | fibrillation | fibrilation)) | ((monitor | smartphone | phone | mobile | mhealth | m-health | ehealth | e-health | app | apps | pocket | portable) +(atrial | atrium | auricular | fibrillation | fibrilation) +(ecg | ekg | ecgs | ekg | electrocardiogram | electrocardiograph | electrocardiograms | electrocardiographs | electrocardiography))

Link

3 results

Appendix A3: PRISMA diagram illustrating EAC literature search

[From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097]



Appendix B: Critical appraisal of clinical evidence

Appendix B1: RCTs (Cochrane Collaboration's tool for assessing risk of bias)

Goldenthal *et al.* 2019 (n=262 randomised; 238 analysed including 115 in intervention arm)

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	"Randomized 1:1 using a blocked randomization scheme to age- match patients in the control and intervention groups."	Low
	Allocation concealment	Not reported. However no difference in baseline characteristics between arms (Table 1)	Low
Performance bias	Blinding of participants and personnel*	Unable to blind; "Patients randomised to the iHEART intervention arm received an iPhone, cellular service plan with unlimited data/text messaging and AliveCor KardiaMobile ECG for 6 months." Standard care not defined.	High (but unavoidable)
Detection bias	Blinding of outcome assessment*	Unable to blind; "upon discovery of any arrhythmia patients contacted their healthcare provider, and all treatment, management, and follow-up for the arrhythmia were determined by the patient's provider."	High (but unavoidable)
Attrition bias	Incomplete outcome data*	Follow-up (at six months) not obtained in five of the control patients.	Low
Reporting bias	Selective reporting	Power calculation included (to detect a hazard ratio of 2 for recurrence detection). Primary and secondary analysis defined. Study not registered. All analysis intention-to-treat.	Low
Other bias	Anything else ideally pre-specified.	National Institute of Nursing Research, Grant/Award Number: R01NR014853	Low

*Assessments should be made for each main outcome or class of outcomes.
Abbreviations: ECG electrocardiogram

Reed *et al.* 2019 (n=243 randomised; 240 analysed including 124 in intervention arm)

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Permuted block randomisation by site. "Blocks were randomly labelled using random number generation with site-specific study participation numbers and sent to each local study team."	Low
	Allocation concealment	Sealed opaque envelopes.	Low
Performance bias	Blinding of participants and personnel*	Intervention arm given standard care plus AliveCor Heart Monitor.	High (but unavoidable)
Detection bias	Blinding of outcome assessment*	Patient emailed ECG to co-ordinating research team. If serious cardiac arrhythmia was identified during study, the central study team contacted the local study team and alerted patient immediately by telephone, referring them urgently to use local emergency department or cardiac electrophysiology service. Potential for bias in healthcare costs (applicable to intervention arm only): If specialist follow-up of the ECG tracing was not required, the local study team wrote to the participant informing them and asked them to arrange follow-up with their general practitioner (GP) who was also contacted with the report.	High (but unavoidable for clinical outcomes)
Attrition bias	Incomplete outcome data*	Lost to follow-up reported (only one in each arm).	Low
Reporting bias	Selective reporting	Trial registration (NCT02783898) and protocol published in Trials. Primary and secondary outcomes reported. Powered to detect proportion difference in AF detection.	Low
Other bias	Anything else, ideally pre-specified.	"Role of the Funding Source: The study was funded by Chest, Heart and Stroke Scotland (Action Research Grant R15/A164; £23,056) and British Heart Foundation (BHF Project Grant no. PG/17/63/33198; £21,347) which included funding for purchasing the devices. MR was supported by an NHS Research Scotland Career Researcher Clinician award. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report." "Availability of Data and Material: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request."	Low

	"Competing Interests: The authors declare that they have no competing interests and no financial interest in the device…AliveCor had no involvement in the study."

*Assessments should be made for each main outcome or class of outcomes.
Abbreviations: AF atrial fibrillation; ECG electrocardiogram.

Guhl *et al.* 2020 (n=120 randomised; 61 to intervention)

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	"computer-generated randomization scheme"	Low
	Allocation concealment	"allocation concealed" but method of concealment not defined	Unclear
Performance bias	Blinding of participants and personnel*	Intervention arm given KardiaMobile device	High (but unavoidable)
Detection bias	Blinding of outcome assessment*	"Study staff, outcome assessors, and data analysts were not blinded to the allocation as the intervention group had additional assessments of the app."	High (but unavoidable)
Attrition bias	Incomplete outcome data*	Loss to follow-up reported, and similar in each arm (four in intervention, three in control)	Low
Reporting bias	Selective reporting	Trial registered (NCT030935558) and pilot published. Primary and secondary outcomes reported. Power calculation reported (based on improvement of HRQoL). All analyses were intention-to-treat.	Low
Other bias	Anything else, ideally pre-specified.	"Acknowledgments This work was supported by the Doris Duke Charitable Foundation Award 2015084 and the National Heart, Lung, and Blood Institute (R01 HL143010)." "Conflicts of Interest None declared."	Low

*Assessments should be made for each main outcome or class of outcomes.
Abbreviations: HRQoL health-related quality of life

Koh *et al.* 2019 (n=236 randomised; 203 analysed including 105 in intervention arm)

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	"Computer-generated simple randomization and was carried out by a contract research organization."	Low
	Allocation concealment	Not reported. However no difference in baseline characteristics between arms (Table 1)	Low
Performance bias	Blinding of participants and personnel*	Intervention is 30 days of KardiaMobile, or 24-hour ambulatory Holter monitor.	High (but unavoidable)
Detection bias	Blinding of outcome assessment*	"All ECGs were adjudicated by an electrophysiologist who was unaware of the patient's demographic and clinical characteristics." However frequency and duration of ECGs differed between intervention (KardiaMobile used three times a day for 30 days) and control arm (single 24-hour Holter).	High (but unavoidable)
Attrition bias	Incomplete outcome data*	23 (18%) excluded from intervention arm, 10 (9%) excluded from control arm, Figure 1.	High
Reporting bias	Selective reporting	Study registered (NCT04332718). "All the authors vouch for the accuracy of the data and confirm that the contents of this article adhere to the specifications in the protocol." Power calculation included (based on proportion difference in AF detection). Primary and secondary outcomes reported.	Low
Other bias	Anything else ideally pre-specified.	"The KardiaMobile and 1 unit of Holter analysis system were purchased for the study. The source of the funding was from the Medical Research Grant, Ministry of Health, Malaysia (NMRR-17-1342-36303). The device manufacturers had no role in the study design, data accrual, or data analysis and had no access to the study data." The authors declared no conflicts of interest.	Low

*Assessments should be made for each main outcome or class of outcomes.
Abbreviations: AF atrial fibrillation; ECG electrocardiogram.

Appendix B2: Diagnostic accuracy studies (QUADAS-2)

Narasimha *et al.* 2018 (n=38 enrolled, 33 included in analysis)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection.

The inclusion criteria were patients aged 18 years or older with palpitations (usually occurring less frequently than once a day) with prior non-diagnostic ECGs or Holter monitoring who demonstrated the ability to use a smartphone device to record and upload a test ECG recording at the office visit.

The exclusion criteria were myocardial infarction within the last three months, known history of sustained ventricular tachycardia (VT) or fibrillation, New York Heart Association class IV heart failure, unstable angina, syncope as the presenting symptom, inability or unwillingness to use the device, and movement disorders including but not restricted to tremors.

It is not clearly described how many patients attended the clinic, nor how the 38 patients were enrolled. Additional risk of bias due to exclusion of individuals unable to use smartphone (which may bias toward younger, wealthier patients).

- Was a consecutive or random sample of patients enrolled? Unclear
- Was a case-control design avoided? Yes
- Did the study avoid inappropriate exclusions? No

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patient (prior testing, presentation, intended use of index test and setting)

Patients presenting with palpitations to outpatient cardiology clinics with a non-diagnostic previous work-up (ECG and in some cases, a Holter monitor) were eligible for the study if their symptoms warranted evaluation with ELRs, generally meaning that symptoms occurred less often than daily but more frequently than several times per month. Patients who met inclusion and exclusion criteria and demonstrated the ability to use the device signed an informed consent to participate in the study.

Included patients match the decision problem.

Is there concern that the included patients do not match the review question? CONCERN: LOW

DOMAIN 2: INDEX TEST

A. Risk of Bias

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes
- If a threshold was used, was it pre-specified? N/A

Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW**

Describe the index test and how it was conducted and interpreted.

The KMs were provided free of charge for the duration of the monitoring period, which ranged from 14 to 30 days. Patients were instructed to transmit ECGs via the KM whenever they had symptoms. In addition, patients also had the option of recording symptoms on the KM app itself, which most patients preferred to do. Recordings from the KM were accessed via a password-protected website. Study personnel viewed these recordings once every 24 hours and notified the physician's office if a serious or sustained arrhythmia (sustained VT defined as a wide complex tachycardia at a rate over 120 beats per minute lasting longer than 30 seconds, sinus pauses more than 3 seconds, high-degree heart block) was detected. The ECG strips were de-identified, and two copies of the recordings were made. Each set of recordings was analysed by two cardiologists participating in the study. If the interpretation of the rhythm strips did not match, the tracings in question were evaluated by a third independent cardiologist. Care was taken to ensure that the same cardiologists did not receive the KM strips and the ELR strips at the same time from the same patient.

Results of intervention and comparator were interpreted at different times by two cardiologists (third for arbitration).

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted

The ELRs (Lifewatch, Rosemont, IL, US) used electrodes and an external monitor worn by the patient with a button to press when symptoms were felt. ELRs were recorded continuously throughout the monitoring period and thus could detect arrhythmias even without patient activation. Patients were being monitored with ELRs according to standard protocol and the physician on call was notified as needed by the ELR company. Similarly, the ELR recordings were provided to two separate cardiologists who were blinded to patient information.

Patient information removed from reference standard and interpreted by two cardiologists.

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**

B. Concerns regarding applicability

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)
Describe the time interval and any interventions between index test(s) and reference standard)

Study included 33 out of 38 enrolled patients (two skin allergy to ELR electrodes, three did not send initial rhythm strip from KM to start transmitting data and did not respond to emails requesting permission to access them). One patient excluded due to Parkinson's with resting tremors (difficult taking KM recordings). Continuous ELR and patient activated KM recorded during same period.

"Compliance with the ELR may have been better if it was used alone for arrhythmia detection. The fact that patients had the KM may have led them to discontinue use of the ELR earlier than they might have otherwise."

Both arms experienced technical issues with 5/38 (13%) excluded from analysis. Patient compliance have influenced analysis.

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

- Was there an appropriate interval between index test and reference standard? Yes
- Did all patients receive a reference standard? Unclear
- Did patients receive the same reference standard? Yes
- Were all patients included in the analysis? No

Could the patient flow have introduced bias? **RISK: HIGH**

William *et al.* 2018 (n=52)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection.

Patients with a diagnosis of AF who were admitted for antiarrhythmic drug initiation (dofetilide or sotalol) were screened for enrolment. Inclusion criteria included male or female patients, aged 35 to 85 years with a history of paroxysmal or persistent AF, with baseline corrected QT interval less than 470 ms or 500 ms if the QRS duration was greater than 120 ms. Patients with pacemakers or defibrillators were excluded.

At risk of bias due to very specific inclusion criteria (QT interval, QRS duration, age range).

- Was a consecutive or random sample of patients enrolled? Yes
- Was a case-control design avoided? Yes
- Did the study avoid inappropriate exclusions? No

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patient (prior testing, presentation, intended use of index test and setting)

Enrolled patients were provided with a Kardia Mobile Cardiac Monitor (KMCM) paired with an iPod at the time of their admission for antiarrhythmic drug initiation. Dofetilide or sotalol were administered twice daily for six monitored doses during admission, with 12-lead ECG recordings performed two hours after each dose. Patients who were in AF after the fourth dose underwent electrical cardioversion. Setting: single clinic

Included patients match the decision problem.

Is there concern that the included patients do not match the review question? CONCERN: LOW

DOMAIN 2: INDEX TEST

A. Risk of Bias

Describe the index test and how it was conducted and interpreted.

Patients were instructed to perform a 30 second recording corresponding to a lead I ECG rhythm strip by placing at least one finger from each hand on the electrodes immediately after each 12-lead ECG recording. The rhythm strip was automatically analysed using the KMCM algorithm. The algorithm generates an interpretation of "normal," "possible atrial fibrillation detected," or "unclassified." The recorded rhythm strips were then automatically transferred to AliveCor's Health Insurance Portability and Accountability Act of 1996–compliant cloud server and were downloaded and printed for review. All 12-lead ECGs and KMCM recordings were independently reviewed by blinded electrophysiologists who classified the rhythm as sinus rhythm, AF, or non-interpretable.

Review by blinded electrophysiologists, low risk of bias.

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes
- If a threshold was used, was it pre-specified? N/A

Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted

Patients were instructed to perform a 30 second recording corresponding to a lead I ECG rhythm strip by placing at least one finger from each hand on the electrodes immediately after each 12-lead ECG recording. All 12-lead ECGs and KMCM recordings were independently reviewed by blinded electrophysiologists who classified the rhythm as sinus rhythm, AF, or non-interpretable.

Review by blinded electrophysiologists, low risk of bias.

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram) Describe the time interval and any interventions between index test(s) and reference standard) KMCM recording immediately after 12-lead ECG. 225 simultaneous 12-lead ECG and KMCM recordings. All diagnostic outcomes reported on per-reading not per patients, so unclear how many patients included in this assessment.

- Was there an appropriate interval between index test and reference standard? Yes
- Did all patients receive a reference standard? Unclear
- Did patients receive the same reference standard? Yes
- Were all patients included in the analysis? Unclear

Could the patient flow have introduced bias? RISK: UNCLEAR

Selder *et al.* 2019 (n=233 enrolled; 226 completed the study)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection.

The study population consisted of all Hartwacht Arrhythmia (HA) patients who submitted a Kardia Mobile (KM) ECG from the start of the program in January 2017 until March 2018. Typically, patients presenting with paroxysmal AF, palpitations of unknown origin or near-collapse were selected by the cardiologists of this clinic to participate in the Hartwacht program, although indications for inclusion in the program were left at the discretion of the physician.

Unclear if patients were referred for 12-lead ECG, and whether this was conducted.

- Was a consecutive or random sample of patients enrolled? Yes
- Was a case-control design avoided? Yes
- Did the study avoid inappropriate exclusions? Unclear

Could the selection of patients have introduced bias? RISK: UNCLEAR

B. Concerns regarding applicability

Describe included patient (prior testing, presentation, intended use of index test and setting)

Prior testing not reported, presentation (registered diagnoses, and anti-arrhythmic medication reported in Table 1). Setting: private outpatient cardiology clinic

Indication for inclusion in the program were left at the discretion of physician, therefore it is unclear whether the cohort matches the decision problem.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2: INDEX TEST

A. Risk of Bias

Describe the index test and how it was conducted and interpreted.

Whenever participants experienced palpitations or related complaints, they were encouraged to record an ECG with the KM device, after which the ECG and its classification by the algorithm were automatically transferred to the patient's electronic patient record. There was no limit to the number of ECGs that could be recorded. Index test is the KM interpretation of the ECG.

Index test results were the KardiaMobile software classification which was conducted before the reference standard (clinician review).

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes
- If a threshold was used, was it pre-specified? N/A

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted
ECGs were assessed by the Hartwacht team, consisting of a supervising cardiologist (0.05 FTE), a specialised cardiology nurse (1.0 FTE) and a doctor's assistant (0.02 FTE), working on weekdays from 08.00 hrs to 17.00 hrs. Furthermore, a cardiologist who could directly access all Hartwacht ECGs was available 24/7 for emergency purposes. Patients received feedback from the Hartwacht team within one working day by phone or email. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated from the KM interpretation, with the Hartwacht team interpretation as reference standard.

Partial comparison (both index and reference test used same ECG).

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: HIGH**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)
Describe the time interval and any interventions between index test(s) and reference standard)
The same ECG trace was used for the index and reference tests. Only seven patients exited the program (3%) mostly because they never made ECGs. A total of 5982 KM ECGs were received, with a median of 28 per patient per year. Duration of follow-up not reported.

- Was there an appropriate interval between index test and reference standard? Yes
- Did all patients receive a reference standard? Yes
- Did patients receive the same reference standard? Yes
- Were all patients included in the analysis? No

Could the patient flow have introduced bias? **RISK: LOW**

Hermans *et al.* 2021 (n=126 enrolled, 115 completed the study)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection.

Patients (18 years and older) who underwent paroxysmal AF ablation from May 2017 to October 2019 in the Maastricht University Medical Centre, The Netherlands, were included in this study. Individuals were excluded if they had no smartphone and were not able to operate the AliveCor Kardia (ACK) system after instructions. Additionally, just a limited number of ACK devices was available, which was a limiting factor in inclusion of patients.

Risk of bias due to need for availability of smart phones (age and wealth may have been), and limited number of KardiaMobile devices which may have influenced patients recruited.

- Was a consecutive or random sample of patients enrolled? Unclear
- Was a case-control design avoided? Yes
- Did the study avoid inappropriate exclusions? No

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patient (prior testing, presentation, intended use of index test and setting)

Baseline clinical characteristics (demographics, medical history and therapy prior ablation) were retrieved from patients' medical records. As a standard of post-AF ablation follow-up care, outpatient clinic visits including Holter monitoring (minimum 24 hours) at three, six and 12 months follow-up were performed.

Included patients match the decision problem.

Is there concern that the included patients do not match the review question? CONCERN: LOW

DOMAIN 2: INDEX TEST

A. Risk of Bias

Describe the index test and how it was conducted and interpreted.

At one of these time points patients were provided with an ACK (AliveCor Inc., Mountain View, CA) simultaneously with Holter and instructed to use the ACK monitor to record 30 s ECG recordings three times daily and in case of symptoms for a period of 4 weeks. Patients were instructed to record an ECG by placing two (index and middle) fingers of each hand on the electrodes of the ACK device. If an ECG recording could not be obtained, different finger positions were allowed. The ACK ECG recordings were sent separately via email to the research team and stored in the hospital electronic database. All ACK ECG recordings were analysed by two researchers experienced in ECG evaluation (A.N.L.H. and M.G) separately and in case of doubt, by a third researcher (N.A.H.A.P) to provide a definite diagnosis. Their diagnosis was considered as the gold standard to assess the sensitivity and specificity of the ACK algorithm. The researchers were asked to rate the ACK ECG recordings as either adequate or inadequate in terms of AF recognition and to make a diagnosis of ECG recordings as 1) sinus rhythm, with or without premature atrial contractions (PAC) or premature ventricular contractions (PVC), 2) AF (defined as a minimum of 30 s of AF), 3) other arrhythmias (including atrial flutter or a regular supraventricular tachycardia) or 4) unreadable. Unreadable ACK ECG recordings were defined as having too much interference (more than 50% of a single 30 s record).

Index test results were the KardiaMobile software classification which was conducted before the reference standard (clinician review).

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes
- If a threshold was used, was it pre-specified? N/A

Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted

At one of these time points patients were provided with an ACK (AliveCor Inc., Mountain View, CA) simultaneously with Holter and instructed to use the ACK monitor to record 30 s ECG recordings three times daily and in case of symptoms for a period of 4 weeks. Holter ECG recordings were collected at three, six or 12 months follow-up. Information relating to the interpretation of the Holter ECGs was not provided.

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)
Describe the time interval and any interventions between index test(s) and reference standard)
Study included 115 out of 126 enrolled patients who submitted KardiaMobile recordings (8.7% excluded with no reasons provided). Monitoring strategies (KardiaMobile and Holter) were evaluated at 3 months in 74 patients (64.3%), 6 months in 16 patients (13.9%), and at 12 months in 25 patients (21.7%).

- Was there an appropriate interval between index test and reference standard? Yes
- Did all patients receive a reference standard? Yes
- Did patients receive the same reference standard? Yes
- Were all patients included in the analysis? No

Could the patient flow have introduced bias? **RISK: LOW**

Appendix B3: Case-control studies (STROBE: case-control studies)

Hickey *et al.* 2017 (n=46; 23 cases, 23 controls)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	"Age and gender matched control patients."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Comparison of mHealth and usual care over 6 month period. Control selection documented. Outcome (AF or AFl) defined. QoL (SF-36v2) included in some cases.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Societal burden of AF, lack of consistent follow-up, need to improve AF detection and treatment.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"The primary outcome of this study was the detection of recurrent AF or other atrial arrhythmias over a 6-month period of time, using the AliveCor ECG as compared to usual cardiac care without mHealth daily monitoring".
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"The control group consisted of 23 age (within 5 years) and gender matched patients with a documented history of AF receiving usual cardiac medical care (no daily ECG self-monitoring) as part of their usual clinical management."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Partially	Departments of cardiac electrophysiology and cardiac ambulatory care (US). Recruitment dates not reported. Follow-up to 6 months.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Yes	Patients aged 21 years old or older, with documented AF, scheduled for cardioversion, ablation or medical management aimed at maintaining normal sinus rhythm. Patients who successfully had normal sinus rhythm restored were given a heart monitor (AliveCor).
		(*b*) For matched studies, give matching criteria and the number of controls per case	Yes	Age (within 5 years) and gender matched. 1 control for each case.

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Partially	Outcomes: QoL (SF-36v2 given to some cases), AF or AFL detection (interpretation undefined). Clinical characteristics, medications and AF procedures also recorded.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	No	It is not reported how outcomes in the control group were determined.
Bias	9	Describe any efforts to address potential sources of bias	Partially	Table 1 comparison shows no difference in clinical characteristics between cases and controls.
Study size	10	Explain how the study size was arrived at	No	Not reported. Noted to be a pilot cohort from a larger randomised trial.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Statistical analyses section methods describes how values have been summarised (mean, SD, frequency, percentage). Groupings not conducted
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	Kaplan-Meier, Fisher's exact test, paired t-test, Cox proportional hazards applied.
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	Groupings not reported
		(*c*) Explain how missing data were addressed	No	Not reported (however missing data is acknowledged in Table 1).
		(*d*) If applicable, explain how matching of cases and controls was addressed	No	Matching criteria reported, but not matching process.
		(*e*) Describe any sensitivity analyses	N/A	No sensitivity analysis reported
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	No	Not reported, but pilot cohort from larger randomised trial.
		(b) Give reasons for non-participation at each stage	No	Not reported, but pilot cohort from larger randomised trial.
		(c) Consider use of a flow diagram	No	Not reported, but pilot cohort from larger randomised trial.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on	Yes	Table 1, but confounding not accounted for.

		exposures and potential confounders		
		(b) Indicate number of participants with missing data for each variable of interest	Partially	Authors acknowledge data missing in Table 1, but missing data not addressed in other analysis.
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Yes	“Over the six month follow-up period, 14 patients in the ECG monitoring group (61%) and 7 patients in the control group (30%) had episodes of AF or AFL detected. Cox proportional hazard model analysis yielded a hazard ratio of 2.55 with a 95% confidence interval of 1.06 to 6.11, p=0.04.”
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Confounding not accounted for.
		(*b*) Report category boundaries when continuous variables were categorized	N/A	Categorical boundaries not included
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No	Results reported as hazard rate.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Subgroup of cases (13 out of 23) with paired QoL (baseline and 6 months).
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	Improved quality of life (spanning both physical and mental health domains). Increased detection of AF and AFl.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Non-randomised, small homogenous group of patients. Larger RCT planned.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	"Cardiac mHealth self-monitoring with the AliveCor™ ECG is a feasible and effective mechanism for improving AF and AFL detection in the real world. Individuals with AF who engaged in self-monitoring and knew their ECGs were vigilantly being reviewed reported a better self-reported QoL."
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Discusses in limitation that this study was conducted in a homogenous group of patients.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Partially	"Disclosures: This research is funded by a R01 from the National Institute of Nursing. NIH/NINR R01NR014853." "Conflict Of Interests: None."

*Give information separately for cases and controls.

Appendix B4: Single-arm observational studies

Dimarco *et al.* 2018 (n=148)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	No	Not reported
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Study time period, symptomatic recordings, clinical diagnoses and time to diagnosis all reported.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Palpitations are a common symptom in general population. Patients present to GP, some referred to cardiologist, a small proportion of which will be an arrhythmia. However can impact quality of life and cause anxiety.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"We sought to examine the acceptability and suitability of the Kardia Mobile as an alternative to traditional ambulatory ECG in the initial investigation of palpitations".
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	KardiaMobile in place of wearable ambulatory ECG monitors.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Single-centre (UK District General Hospital) between March 2015 and June 2016. Median period of use reported in results.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	"Inclusion criteria were patients referred to a cardiologist for investigation of palpitations occurring less than daily with a) access to a compatible smartphone and b) willingness and ability to use a device. Patients with a history of syncope were excluded."
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give	Yes	"Initial interpretation of recordings made by a cardiac physiologist, with diagnosis confirmed by a cardiologist.

		diagnostic criteria, if applicable		Data regarding patient demographics, symptoms and correlating rhythm were collated”
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	“Use of the device continued until a symptom-rhythm correlation was established and ECG diagnosis made”
Bias	9	Describe any efforts to address potential sources of bias	No	None described
Study size	10	Explain how the study size was arrived at	No	Not explicitly described (but patient throughput is implied)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	No	Not conducted
		(*b*) Describe any methods used to examine subgroups and interactions	No	No subgroup analysis
		(*c*) Explain how missing data were addressed	No	Missing data not addressed
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Not reported
		(*e*) Describe any sensitivity analyses	No	None conducted.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Partially	Two patients lost to follow-up. However number screened, and those eligible for inclusion not reported.
		(b) Give reasons for non-participation at each stage	Yes	One patient returned device before diagnosis due to high-pitched sound from device, and one misplaced device.
		(c) Consider use of a flow diagram	No	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Gender, age, period of device use and total number of patients taking symptomatic recordings reported
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported

		(c) Summarise follow-up time (eg, average and total amount)	Yes	Median period of use 244 days (range 4 to 484 days)
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	AF detection, time to AF diagnosis
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	No other analysis
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	Correlation of symptoms with heart rhythm in 76% of individuals. Early detection of AF. Patients were also reassured and further investigations avoided.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Limitations of device stated: “lower rate of smartphone usage in the older population. Only two patients in our cohort were aged 75 years or over. Patients also need to follow the correct procedure to record interpretable ECGs.”
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	“We plan to expand this service to primary care providers in our locality and further evaluate this hypothesis”
Generalisability	21	Discuss the generalisability (external validity) of the study results	No	Not reported
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Partially	Funding source not reported. “Conflict of interest: None declared.”

*Give information separately for exposed and unexposed groups.

Bray *et al.* 2021 (n=74)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Service evaluation
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Setting, 6 month duration, physician interpreting the ECG rhythm strips
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	"Community follow-up monitoring is necessary to guide effective treatment. Conventionally, 12-lead ECGs have been used, but the advent of reliable single-lead ECGs with accurate built-in AF detection algorithms have the potential to streamline this monitoring process."
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"This pilot initiative aimed to test the feasibility of integrating a single-lead hand-held ECG system, the AliveCor, into community monitoring of treatment in patients with recently diagnosed fast AF and opportunistic community diagnosis of AF."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"This evaluation of a clinical service improvement pathway"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Patients from the Neath Port Talbot community referred to the Acute Community Team between June and November 2017.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	"Participants were eligible for inclusion if patients had been referred to the Acute Community Team with (1) known fast AF requiring monitoring and management, and (2) suspected AF due to an abnormal pulse on manual pulse check. There were no specific exclusion criteria." Unsure if patients had scheduled community attendances or attended when symptomatic.
		(*b*) For matched studies, give matching criteria and	N/A	

		number of exposed and unexposed		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Outcomes reported separately for community AF monitoring, and community AF diagnosis.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Not described in method (but is in results: Table 2)
Bias	9	Describe any efforts to address potential sources of bias	No	None described
Study size	10	Explain how the study size was arrived at	Yes	Not explicitly described (but patient throughput is implied by service evaluation design)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Figure 2 bar chart of frequency of use only.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	Descriptive statistics only (software used named)
		(*b*) Describe any methods used to examine subgroups and interactions	Partially	Two groups described, however assume overlap (37+53=90 not 74 as reported in abstract and methods)
		(*c*) Explain how missing data were addressed	No	Missing data not addressed
		(*d*) If applicable, explain how loss to follow-up was addressed	Yes	“No participants were lost to follow-up”.
		(*e*) Describe any sensitivity analyses	No	None conducted.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	Not explicitly reported, but implied from service evaluation design and reported no loss to follow-up
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	No	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Partially	Table 1 (Gender, age). No results from routine bloods, comorbidities, medication or symptoms included.

		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported
		(c) Summarise follow-up time (eg, average and total amount)	Partially	Each patient was followed up to 6 months, however mean duration not reported.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	Number of iECG, number of patients requiring 12-lead ECG, AF detection.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	No other analysis
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	"AliveCor device was easy to use, more time-effective and cost-effective, and successfully prevented the need for serial 12-lead ECGs in the community. Of the 37 patients requiring ECG monitoring, 113 iECGs were needed and of the 53 patients with an 'abnormal' pulse, 15% were found to be in new-onset AF and were appropriately anticoagulated."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Small sample size, and single health board. Verbal consent instead of written limited collection of patient data.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	"Integration of single-lead ECG devices into existing pathways has been demonstrated to be feasible in primary care, opportunistically in pharmacies, in low-resource settings, in rural areas and on a large scale."

Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Single health-board
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	“Funding ; The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Competing interests: None declared.”

*Give information separately for exposed and unexposed groups.

Reed *et al.* 2021 (n=68 referred; 54 given device, 50 analysed)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	No	Study design not reported
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Time period, setting, and outcomes all reported.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	High number of ED and GP presentations due to palpitations, but difficulty in diagnosing if symptoms are infrequent.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"This study reports the subsequent establishment of a smartphone palpitation and pre-syncope ambulatory care clinic (SPACC)."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	Change to pathway. Eligible patients were offered an appointment at new clinic.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Ambulatory care clinic, Edinburgh, referrals between 22/07/2019 and 31/10/2019, KardiaMobile, follow-up assumed to be for 90 days, with early review at 28 days to allow prompt treatment, data collection on REDCap.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Partially	"all patients aged 16 years or older presenting to the ED or Acute Medicine Unit (AMU) of the Royal Infirmary of Edinburgh (RIE) with palpitations or pre-syncope, whose ECG was normal, who had a compatible Apple or android phone, tablet, or watch, and in whom an underlying cardiac dysrhythmia was possible". "Exclusion criteria included the patient being non-ambulant, requiring hospital admission, having a prior diagnostic ECG, having multiple frequent episodes or recent acute myocardial infarction (AMI), severe heart failure, or unstable angina, having associated chest pain or syncope, being unwilling or unable to use the AliveCor Heart Monitor and ECG App,

				having a cardiac pacemaker or other implanted electronic device, or having a likely non-cardiac cause for their palpitations (for example, anxiety, sepsis).” Review at 4 weeks, method of review unclear (but in results assume this is via another visit at clinic).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Symptomatic rhythm (routine bloods also taken), patient diary. Interpretation of KardiaMobile not defined in methods (but assumed by healthcare professional in Results)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Partially	Automated categorisation of KardiaMobile not described in Methods.
Bias	9	Describe any efforts to address potential sources of bias	No	None described
Study size	10	Explain how the study size was arrived at	No	Not described (all eligible patients during the study period were offered a referral)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	No	Routine bloods taken but no description of how these were handled.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	No	No statistical analysis described
		(*b*) Describe any methods used to examine subgroups and interactions	No	No subgroup analysis or interaction analysis
		(*c*) Explain how missing data were addressed	No	Missing data not addressed
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Loss to follow-up not described in methods (but data flow-diagram indicates the number who did not attend follow-up appointment).
		(*e*) Describe any sensitivity analyses	No	None conducted.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers	Yes	Data flow diagram (Figure 1), 50 out of 68 underwent full investigation.

		potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage	Yes	Data flow diagram (Figure 1)
		(c) Consider use of a flow diagram	Yes	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Partially	Table 1 (Gender, age, symptom and duration). No results from routine bloods, comorbidities, medication included.
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported
		(c) Summarise follow-up time (eg, average and total amount)	No	Assume length of time between clinic appointments represents the follow-up time per patient: median 28 days [Q1:Q3, 15.25 to 30] days (one patient appears to have had 76 days)
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	AF detected in 2 patients (3%).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Time to diagnosis not captured.
		(*b*) Report category boundaries when continuous variables were categorized	N/A	Categorical outcomes are diagnoses following interpretation of KM ECG by an ED clinician.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	No comparator arm
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	No other analysis
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	"Our preliminary three-month clinic data show that the detection of symptomatic cardiac dysrhythmia in 8.8% of patients is comparable to the 8.9% of patients who had a symptomatic cardiac dysrhythmia detected in the IPED study and show that a research protocol and

				research finding can be successfully extrapolated and implemented in a pragmatic clinical setting.”
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	No	Although authors stress results are preliminary. Difficulties addressed and improvements made are reported in the results section.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Partially	Limitations not addressed, however implementation in a pragmatic clinical setting, expansion to GP referrals and ability to support this service model around UK are highlighted.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Compares results to the IPED RCT.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	“Funding: MR is supported by an NHS Research Scotland Career Researcher Clinician award. The REDCap database used for this study was funded by a Royal College of Emergency Medicine grant.” “Conflicts of Interest: All authors declare that they have no competing interests and no financial interest in the device used in this study. AliveCor had no involvement in the study. The Emergency Medicine Research Group Edinburgh received sponsorship for the EMERGE10 conference in 2018 from various companies including AliveCor.”

*Give information separately for exposed and unexposed groups.

Praus *et al.* 2021 (n=43)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	No	Study design not described
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Intervention and outcomes reported.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Healthcare resource and economic burden of AF.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"The purpose of this nurse practitioner (NP)–led quality improvement project was to improve patient outcomes, decrease resource utilization, and reduce anxiety related to AF through the use of a personal, single-lead electrocardiogram (ECG)."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"An NP…conducted a quality improvement project"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Partially	Cardiology division of a large multispecialty group which is a subsidiary of a national healthcare organisation. Location not stated but assumed to be US. Recruitment period not stated, "Enrolment and distribution of the KM devices occurred over several weeks". "Patients were followed for eight weeks and instructed to record and email an ECG at least once daily as well as when symptomatic."
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	"Eligibility criteria included adult patients who (1) had two or more AF-related ED or UC visits in the past 12 months, (2) needed rate control with medication titration, or (3) needed monitoring for AF reoccurrence after re-establishing sinus rhythm—either by chemical or direct current cardioversion. Additionally, participants needed to be established with the clinic, able to understand and

				consent to participation, and have comfort using the personal ECG device and application on their smartphone. Forty-three patients were identified and participated in the project." Patients followed for 8 weeks. "An NP would review the ECGs daily. Patients were aware that ECGs would be read Monday through Friday between the hours of 8:00 a.m. and 5:00 p.m.; patients were advised to proceed to an UC or ED if symptomatic outside of those hours. If the recordings were normal, daily transmissions continued. If abnormal, attempts were made to contact the patient within an hour of ECG review, by telephone or email; once contact was made, the patient was offered a NowClinic visit, although most were comfortable with telephone follow-up."
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	KardiaMobile and NowClinic (telehealth platform to enable patients to log in for a face-to-face visit).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Outcome from Kardia app used, those considered unclassified were reviewed by the NP. Patients instructed to record ECG once daily and whenever symptomatic. Patients with abnormal readings were contacted by phone or email. Patient survey regarding ease of use, satisfaction recorded at end of study. Hospital Anxiety and Depression Scale (HADS) recorded at week 1 and week 8.
Bias	9	Describe any efforts to address potential sources of bias	No	Not reported
Study size	10	Explain how the study size was arrived at	No	Not reported, identified in abstract as "a convenience sample".
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	No	Not reported

		describe which groupings were chosen and why		
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	No	"Statistical testing could not be conducted given the small number of participants."
		(*b*) Describe any methods used to examine subgroups and interactions	No	No subgroup analysis
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Not reported
		(*e*) Describe any sensitivity analyses	No	None conducted
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	No	Not reported
		(b) Give reasons for non-participation at each stage	No	Not reported
		(c) Consider use of a flow diagram	No	No data flow
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Partially	Table 1 (age, gender, ethnicity, distance of residence from practice) however comorbidities, medication not recorded.
		(b) Indicate number of participants with missing data for each variable of interest	No	Number of ECGs reported, however not reported how many patients these refer to (would have to assume all 43 patient submitted ECG).
		(c) Summarise follow-up time (eg, average and total amount)	No	Exact length of follow-up not reported, other than to say patients were followed for eight weeks.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	Reports results of 1501 ECGs, 537 were possible AF and of these, 74 had rapid ventricular rates. Number of unclassified and their breakdown also reported.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Not reported
		(*b*) Report category boundaries when	No	Not reported

		continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No	No comparator arm
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	No	None conducted
Discussion				
Key results	18	Summarise key results with reference to study objectives	No	No mention of health related outcomes in Discussion.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Single-centre, may not have representative patients. "Statistical testing could not be conducted given small number of participants." Need for project with longer follow-up
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Partially	No comparison with other studies. Need for further research highlighted (larger sample, and inclusion of all potential use cases)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	"The project involved a single cardiology practice and may not be representative of patients in other practices or geographic locations."
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	"Competing interests: M. Proenza obtained funding from Southwest Medical, part of OptumCare for the Kardia-Mobile devices, and coordinated with Southwest Medical's IT department."

*Give information separately for exposed and unexposed groups.

Lowres *et al.* 2020 (n=32 recruited; 29 completed self-monitoring)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	"Pilot study" is in title and abstract. Cross-sectional feasibility study is in Methods.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Patient flow is described explicitly, outcomes reported clearly. Conclusion highlights need for further research.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	New-onset AF (secondary AF) is common and associated with poor prognosis.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"Therefore, this study aimed to assess the feasibility of 1) identifying patients with a transient episode of secondary AF that reverted to sinus rhythm prior to discharge; and 2) patient self-monitoring for AF recurrence after discharge using a handheld ECG device."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"prospective, feasibility study using a cross-sectional design"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Three tertiary hospitals sites in Australia (all named with recruitment dates stated separately for each). Baseline assessment by nurse. Participants asked to record ECG 3 times a day (KardiaMobile) for 4 weeks after discharge. Follow-up with nurse at 4 weeks. All participants invited to participate in semi-structured interview covering user experience. Final phone call at 3 months.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	"The study recruited patients with an episode of new-onset AF secondary to hospitalisation for either non-cardiac surgery or non-cardiovascular acute medical illness. Patients were eligible if they were 1) admitted to hospital in sinus rhythm with no prior history of AF; 2) reverted to sinus rhythm prior to discharge (spontaneously or via cardioversion); 3) 18 years or older; and 4) able to

				provide informed consent. Patients were excluded if they were non-English speaking; or were unable to be contacted by phone following discharge." "To identify patients with secondary AF, we used a progressively modified case finding strategy at each of the three hospital sites. We commenced with a strategy that most closely resembled standard practice at the first site, and then added additional nursing staff resources at the second two sites." Follow-up methods described in detail.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	Not matched
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	All primary and secondary outcomes reported.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	"Each participant was provided with an AliveCor KardiaMobile ECG and Huawei Y560 smartphone for four weeks and taught how to record their own 30 second ECG recording. Participants were asked to record their own ECG 3 times each day, for 4 weeks commencing after hospital discharge."
Bias	9	Describe any efforts to address potential sources of bias	Yes	"Due to the small sample size we did not statistically compare the groups with and without AF recurrence."
Study size	10	Explain how the study size was arrived at	Yes	"As the primary outcome was feasibility and acceptability, a power calculation was not performed."
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Described in statistics section
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	All statistical tests described, power calculation not performed.
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	Some analysis reported separately in results by AF recurrence and no recurrence

				outcomes. “Due to the small sample size we did not statistically compare the groups with and without AF recurrence.”
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Not reported
		(*e*) Describe any sensitivity analyses	No	Not conducted
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	16,454 screening, 224 had secondary AF, 94 were eligible for recruitment, 32 were recruited and 29 completed the self-monitoring.
		(b) Give reasons for non-participation at each stage	Yes	In Fig 1, Case Finding, and Participant self-monitoring.
		(c) Consider use of a flow diagram	Yes	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Yes	Numbers of participants with self-reporting completed at 4 weeks, between 3 and 4 weeks, between 1 and 3 weeks, less than 1 week all reported. 16 completed a semi-structured interview.
		(c) Summarise follow-up time (eg, average and total amount)	Yes	Fig 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	12 out of 29 diagnosed with “possible AF” by the device. “AF recurrence was first identified at a median of 6 days (range 2 to 23 days) post discharge with 9 or 10 recurrences occurring in 9 days or less. “ “Ten of the 12 participants followed instructions and sought medical review prior to the 4-week follow-up, and all were confirmed with AF recurrence”
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders	Yes	Recurrence incidence 34% [95%CI 18% to 54%]

		were adjusted for and why they were included		
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	No comparator arm
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Change to clinical management, CHA2DS2-VA score, HASBLED
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	"Self-monitoring detects a high rate of recurrent AF, most of which occurs within 9 days of discharge. Most recurrences were asymptomatic and many individuals with recurrence were at high risk of stroke." "Our results indicate self-monitoring with a hand-held ECG is feasible, that patients can easily manage the technology, and they experience a sense of security using it."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	"Furthermore, the study population may be biased, through self-selection, towards a sample more familiar with using a smartphone. The incidence of secondary AF identified on the wards is likely underestimated due to probable under-reporting of secondary AF episodes and a lack of routine comprehensive screening, thus the sample may be biased towards patients with symptomatic AF."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Compared detection rate and incidence of secondary AF with other studies.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Clinical implications section, need for further research to investigate the incidence of secondary AF, rate of recurrence after discharge,

				prognostic implications of AF recurrence.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	“Funding This study was funded by a National Heart Foundation of Australia, Vanguard Grant (101011). Nicole Lowres is funded by a New South Wales Health, Early Career Fellowship (H16/52168).”

*Give information separately for exposed and unexposed groups.

Yan *et al.* 2020 (n=1079)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	"Prospective multi-centre observational study" in abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Interventions and outcomes reported clearly.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Poor adherence to Holter monitor, cost and adverse events associated with implantable cardiac monitoring devices, ECG monitoring patches cause irritation.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"The aim of our study was to compare the detection rates of PAF [paroxysmal AF] by a pragmatic strategy of nurse-led intermittent iECG re-cordings during routine clinical observations, with the current standard 24-hour Holter monitoring where available in an international patient cohort hospitalised in a stroke unit with acute ischemic stroke or TIA."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	First line in methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	8 participating centres, all named (Australia and China). Eligibility screening between 2015 and 2018. Consecutive patients underwent iECG with KardiaMobile during routine observations (typically every 2 to 4 hours). All patients received 12-lead ECG. Patients underwent inpatient or outpatient Holter monitoring at discretion of treating stroke team, according to their usual practice. All 'possible AF' traces were reviewed immediately. Reported only in Discussion section: "Any uncertain AF traces following review by the attending physician were reviewed by three experienced physicians."

Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	"Patients were eligible for enrolment if they presented with ischemic stroke or TIA with no known AF, and no AF on the admission 12-lead ECG. Patients were excluded if the treating medical team considered long-term oral anticoagulation use inappropriate because the stroke was very severe, or in the light of other co-morbidities."
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	Not matched
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Primary and secondary outcomes reported. Patient characteristics also recorded.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Measurement methods all defined with primary and secondary outcomes.
Bias	9	Describe any efforts to address potential sources of bias	No	Not reported in methods, but some attempt made in results to address potential source of bias relating to identical results for the number of recordings and days monitored for those with AF detected on iECG and those without AF detected.
Study size	10	Explain how the study size was arrived at	Yes	Pragmatic study recruiting consecutive patients.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	No	None reported
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	Statistical analysis and software described, McNemar's test used to compare proportion of patients with AF detected on iECG versus Holter.
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	Patients split by whether they also underwent Holter monitoring or not.
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Not reported

		(*e*) Describe any sensitivity analyses	No	Not reported
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Partially	"Of the 294 patients who underwent both 24-hour Holter and iECG monitoring, two did not provide their age, and five had missing Oxfordshire score. Forty-one (14%) were lost to follow-up and two died before 3 months." Number screening and number eligible not reported.
		(b) Give reasons for non-participation at each stage	No	Not reported
		(c) Consider use of a flow diagram	Yes	Fig 3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Yes	"*Whole group: 5 patients were missing for age, 3 for sex and 26 for Oxfordshire score; †Holter: 2 patients missing for age, 5 missing for Oxford; ‡No Holter: 3 missing for age, 3 missing for sex and 21 missing for Oxfordshire score."
		(c) Summarise follow-up time (eg, average and total amount)	No	Not reported (can only assume all were followed to 3 months).
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	iECG detected AF in 25 out of 294 patients (8.5%) in the primary analysis while Holter monitor detected 8 (2.8%). Anticoagulation therapy at 3 months reported.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Not reported.
		(*b*) Report category boundaries when continuous variables were categorized	No	Not reported
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No	No comparator group
Other analyses	17	Report other analyses done—eg analyses of	Yes	Anticoagulant therapy at 3 months reported

		subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	“We showed that this strategy after ischemic stroke or TIA, identified new AF in significantly more patients (8.5%) than 24-hour Holter monitoring, which identified AF in only 2.8%, and identified AF earlier.”
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Not simultaneous recordings. Only a quarter had both Holter and iECG. Holter monitoring was only for 24 hours (not 7 days as conducted in other studies)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Reports consistency with other studies.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Implications for clinical practice. Inexpensive, and required only basic training. Automated algorithm permits expeditious AF diagnosis, and easy specialist over-read. Reports geographical variation in practice.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	“Disclosure: This study was supported by a small grant from Boehringer Ingelheim.”

*Give information separately for exposed and unexposed groups.

Lowres *et al.* 2016 (n=42)

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	No	"Feasibility" mentioned in abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Intervention, and outcomes reported clearly.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	High incidence of post-operative AF (after cardiac surgery).
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"We performed this study to determine the feasibility of patients self-monitoring with an iECG to identify recurrence of AF in the post-discharge period following cardiac surgery, and to determine if providing a brief inpatient AF education programme improves patient knowledge of AF and its related health risks, symptoms and medical management."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"This feasibility study used a cross-sectional study design"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Between March 2014 and July 2015, at two hospitals in Australia. AliveCor (iECG) for 4-week period post hospital discharge. Patients requested to take iECG 4 times a day and when

				symptomatic. iECG reviewed by algorithm. If AF identified the participant was contacted to arrange follow-up with treating physician. Participants were telephoned once or twice during the 4-week period to ensure no difficulties using iECG. On completion AF knowledge and postoperative complication were reassessed. Participants were also invited to participate in a semi-structured interview to explore their experience.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	"we recruited cardiothoracic surgery patients who experienced a transient episode of POAF following cardiac surgery; with no history of AF prior to admission; who reverted or were cardioverted to stable sinus rhythm prior to discharge; and were aged 18 years or older. Patients were approached and assessed during their inpatient admission." Methods of follow-up described above.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	Not matched
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Primary and secondary outcomes listed in Table 1.

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Described above
Bias	9	Describe any efforts to address potential sources of bias	No	Not reported
Study size	10	Explain how the study size was arrived at	Yes	"A sample size of 50 participants was chosen to maximize the probability of reaching data saturation during thematic analysis of the interviews and during review of process measures such as reasons for declining participation."
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Described in statistical considerations section
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	In Statistical considerations section
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	"Within subject differences between baseline and follow-up were analysed".
		(*c*) Explain how missing data were addressed	Yes	Missing at random analysis conducted.
		(*d*) If applicable, explain how loss to follow-up was addressed	Yes	"Analysis was limited to complete cases to avoid artificially increasing precision around the estimates by imputing values or carrying baseline values forward."
		(*e*) Describe any sensitivity analyses	No	Not conducted
Results				
Participants	13*	(a) Report numbers of individuals at each	Yes	42 out of 44 participants recruited

		stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		to the study completed the intervention. Fig 2
		(b) Give reasons for non-participation at each stage	Yes	Fig 2
		(c) Consider use of a flow diagram	Yes	Fig 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported
		(c) Summarise follow-up time (eg, average and total amount)	No	However all patients not followed up to 4 weeks were removed, (so can assume included patients had full 4 week follow-up).
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	AF detected in 10 out of 42.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes	24% (95% CI, 12–39%) with AF recurrence within 17 days
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No	No comparator
Other analyses	17	Report other analyses done—eg analyses of subgroups and	Yes	Patient knowledge of AF, device acceptability, ease of

		interactions, and sensitivity analyses		use, compliance, benefits, barriers all reported.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	24% (95% CI, 12–39%) with AF recurrence within 17 days
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Short follow-up, poor quality iECG due to interference in some rural areas.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	"The results of this study should be interpreted with caution, as the sample size was small due to its design as a feasibility study."
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	"It is also likely self-monitoring with the iECG would be feasible in other populations, such as patients who have had catheter or surgical ablation, or other antiarrhythmic interventions including pharmacological therapy. It would also be feasible to use this technique in future studies investigating whether POAF may occur after discharge post-cardiac surgery in the absence of an inpatient episode of POAF."
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	"Funding: This work was supported by a competitive grant from the Cardiothoracic Surgery Research and Education Fund, Sydney Medical School Foundation,

	University of Sydney. AliveCor provided ECG Heart Monitors for study purposes: the investigators are not affiliated with, nor have any financial or other interest in AliveCor.”

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix C: Adverse events

Results of EAC search on MAUDE database (conducted 13/04/2021).

Date of Event	Event Type	Device Problem	Summary
08/09/2020 (FDA report received on 19/10/2020)	Injury	Incorrect, inadequate or imprecise result or readings on KardiaMobile-6L device	KardiaMobile-6L readings were normal, user suffered cardiac arrest and survived. Long QT was the precursor to cardiac arrest. Users did not understand device algorithm could not detect long QT syndrome which may have delayed seeking medical treatment due to normal KM-6L results. Concluded device did not contribute to cardiac arrest and incident was due to user error.
19/05/2020 (FDA report received on 01/07/2020)	Injury	Incorrect, inadequate or imprecise result or readings on KardiaMobile-1L device	KardiaMobile-1L reading was normal whilst patient experiencing a heart attack. Reading did not delay user in seeking medical attention. KM-1L is not intended to detect an infarct or st elevation. Device likely had no malfunction and did not cause or contribute to heart attack. Incident due to user error.
22/04/2020 (FDA report received on 22/05/2020)	Injury	Incorrect, inadequate or imprecise result or readings on KardiaMobile-1L device	User experiencing heart attack with normal KM-1L sinus rhythm. User did not delay seeking medical attention due to result. ECG from user sent to cardiologist and they concurred it demonstrated normal sinus rhythm. KM-1L not intended to detect heart attack and device had not malfunctioned. It did not cause or contribute to heart attack. Incident due to user error.
Unknown, initial report date of 04/02/2020 (FDA report received on 03/03/2020)	Injury	Defective device – KardiaMobile-1L	ECG determined normal sinus rhythm whilst patient experiencing heart attack. It is unknown whether the user delayed seeking medical attention due to this result. Device likely had no malfunction and did not cause or contribute to heart attack. Incident was a result of user error.
Unknown, initial report date of 04/06/2019 (FDA report received on 06/09/2019)	Injury	Therapeutic or Diagnostic Output Failure on KardiaMobile-1L	User recorded a normal sinus rhythm using KM-1L whilst experiencing ‘100% LAD blockage’. The user delayed seeking medical attention due to this result. KM-1L is not intended to detect heart attack or ST elevation. Device likely had no malfunction and did not cause or contribute to heart attack. Incident due to user error.
02/07/2016 (FDA report received on 11/07/2016)	Injury	Incorrect interpretation of signal, device operates differently than expected – AliveCor iPhone 4/4S Case	One user software reported receiving ‘excessive noise’. Some readings showed atrial fibrillation using the software algorithm. Readings were brought to the user’s cardiologist who interpreted it as normal sinus rhythm with artefact which was incorrectly labelled as AF. This resulted in the user having a panic attack. The user also had

			previous error in report readings from AliveCor. The user states the negative impacts caused by the device have been unnecessary healthcare costs and panic attacks. No AliveCor response mentioned in report.
30/10/2016 (FDA report received on 01/11/2016)	Malfunction	Display or visual feedback problem – Kardia personal EKG	User determined that the Kardia ECG doubles heartrate. Received report from AliveCor cardiologist with a warning and immediate physician evaluation strongly advised. One doctor (not specified speciality) reviewed the ECG and stated high heart rate was due to t-wave over sensing. No AliveCor response mentioned in report.
16/04/2015 (FDA report received on 20/04/2015)	Malfunction	Application Network Problem – AliveCor heart monitor	User stated that from some point in 2015 every ECG result was reported as 'we could not classify this ECG'. Customer service claimed this was due to new version of the app. One rep said this message was reported with a low pulse. User stated that many users have low pulse due to metoprolol to control AFib. No AliveCor response mentioned in report.
Abbreviations: AF Atrial Fibrillation; ECG Electrocardiogram; KM Kardia Mobile; LAD left anterior descending (artery).			

Appendix D: Ongoing studies

Full details of ongoing studies (if applicable).

Include hyperlinks to entries on clinical trial databases.

Appendix D1: Ongoing studies identified by company which were excluded by EAC

Trial registration number	Title	Exclusion reason
NCT03515057	Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics (VITAL-AF)	Screening
NCT03940066	Evaluation of Ambulatory Monitoring of Patients After High-risk Acute Coronary Syndrome Using Two Different Systems: Biomonitor-2 and Kardia Mobile (Monitor-ACS)	Implantable cardiac devices (contraindicated
NCT03761394	Pulsewatch: Smartwatch Monitoring for Atrial Fibrillation After Stroke	Comparing smartwatch to KardiaMobile (incorrect comparator)
NCT04332718	Smartphone Electrocardiogram for Recording Atrial Fibrillation After a Cerebral Ischemic Event (SMART-AF)	Already published (Koh *et al.* 2021)
ACTRN12616001293459	Detecting atrial fibrillation, a common heart rhythm abnormality and preventable cause of devastating strokes, using smartphones in patients admitted to hospitals with strokes (SPOT-AF)	Already published (Yan *et al.* 2020)
ACTRN12619000793112	Smart phone based single lead ECG versus traditional ambulatory Holter monitoring to aid diagnosis of cardiac arrhythmias in patients with rapid heart rhythms (WAHOO)	Includes KardiaBand
Not reported (unknown)	Home-based ECG-detection of arrhythmia with ambulatory recorded ECG.	Could not be identified from trial databases (clinicaltrials.gov, Cochrane CENTRAL, Australian New Zealand Clinical Trials Registry)

Appendix D2: Ongoing studies included by EAC

Study title, reference	Status, estimated completion	Study Design	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Health eHeart BEAT-AFib - Health eHeart Biomarkers of Early Atrial Transformation in Atrial Fibrillation [BEAT-AFib; NCT04404465] US	Status: Enrolling by invitation Estimated completion date: September 2040 Last update: September 2020	Observational cohort: n=3,000 3 arms: - control, - at risk of AF, - AF	Inclusion Criteria: 18 years of age or older; English speaking; Able to consent. Any one of the following criteria: A history of non-valvular AF or AFL documented on ECG or ambulatory monitoring within 1 year of enrolment; Two or more of the following criteria if no history of AF: Age over 65 years of age, A diagnosis of hypertension, A diagnosis of diabetes, A diagnosis of sleep apnoea, BMI of 30 or more, Stable HF with preserved or reduced ejection fraction (NYHA Class I, II or III), CKD not requiring dialysis; More than 5% PAC burden on ambulatory ECG monitoring (Holter, Ziopatch, Lifewatch, and so on.); Patients undergoing EP study or ablation for SVT with no history of AF and not meeting any of the above criteria. Exclusion Criteria: Life expectancy less than 1 year; Reversible causes of AF (for example, post-operative AF, cardiac surgery, pulmonary embolism, untreated hyperthyroidism); Pregnant at the time of enrolment; Unwilling or unable to perform follow-up using digital follow-up; CKD requiring	Development of new onset AF [At Risk Group] [10 years]; Progression of AF [AF Group] [10 years].	Recurrence of AF after treatment with direct current cardioversion or AF ablation [AF Group] [10 years]; Symptom Burden [AF Group] [10 years];

			dialysis; Presence of a condition or abnormality that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the data; Patients undergoing active treatment for cancer or diagnosed with cancer requiring treatment in the last 2 years.		
Implementation of High Definition Screening Using Handheld Imaging and Digital Health Technologies Within a Learning Health System to Identify Cardiovascular Disease at the Point-of-care: The ASE-INNOVATE Program [ASE-INNOVATE; NCT03713333] US	Status: Unknown Estimated completion date: October 2019 Last update: October 2018	Interventional (randomised): n=500 2 arms: - Technology-enabled visitations with digital health device diagnostics. - Standard-care visitations (handheld imaging and digital health screening after patient-physician encounter)	Inclusion criteria: All participants of the ASE 2018 Outreach Event who are at least 18 years old who are referred for a cardiac evaluation. Exclusion Criteria: Those not willing to consent.	Patient-reported outcome measures; patient-reported experience measures; health economic outcomes.	Number of referrals for mobile cardiac telemetry; number of referrals for diagnostic imaging with TTE; incidence of heart failure; incidence of AF; emergency department visitations for a cardiac condition; hospitalization for a cardiac condition; presenting for a clinical visitation for a cardiac condition; percentage of patients initiating medical therapy for a cardiac condition.
Individualized Studies of Triggers of Paroxysmal Atrial Fibrillation [I-STOP-AFib; NCT03323099] US	Status: Completed (no publication) Estimated completion date: April 2020 Last update: Feb 2021	Interventional (randomised): n=500 2 arms: - Eureka mobile application and AliveCor device, “N-of-1” including 3 periods of trigger exposure and 3 period of trigger	Inclusion: patients aged 18 years or older, with symptomatic paroxysmal AF and a smartphone. Exclusion: non-English speakers, children (aged less than 18 years), patients with plans to substantially change AF management over the ensuing 6 months, unwilling to test AF triggers, patients who have had an AV node or AV junction ablation.	Atrial fibrillation quality of life [10 weeks]	

		elimination each lasting 1 week - Eureka mobile application and AliveCor device.			
Validation of a Novel Smartphone-based Photoplethysmographic Method for Ambulatory Heart Rhythm Monitoring in Connection to Treatment of Atrial Fibrillation with Direct Current Cardioversion [NCT04300270] Sweden	Status: Recruiting Estimated completion date: December 2021 Last update: February 2021	Observational cohort: n=480 2 arms: - Participants in validation of smartphone PPG and ECG recordings - Participants in clinical implementation of smartphone PPG and ECG recordings	Validation cohort: Inclusion criteria: Patients aged 18 years and older undergoing direct current cardioversion successfully for treatment of atrial fibrillation or atrial flutter and have a normal heart rhythm after the treatment. Exclusion Criteria: Patients with implantable cardiac devices. Clinical implementation cohort: Inclusion Criteria: Patients aged 18 years and older planned for direct current cardioversion for treatment of atrial fibrillation or atrial flutter. Exclusion Criteria: Patients with implantable cardiac devices; Patients with a spontaneous return to sinus rhythm diagnosed at a screening visit 2 to 4 weeks prior to the scheduled treatment with direct current cardioversion.	Performance of the novel smartphone-based photoplethysmographic method for heart rhythm diagnostics and discrimination of atrial fibrillation from normal heart rhythm [Daily measurements during 30 days].	Independent predictors for recurrence of atrial fibrillation within 30 days of treatment with direct current cardioversion; Predictors for recurrence of atrial fibrillation within 30 days of treatment with direct current cardioversion using deep learning and machine learning techniques; Participant compliance for recording heart rhythm with the novel smartphone-based method twice daily for 30 days; Correlation between patient self-reported symptoms and recorded heart rhythm [30 days]; Proportion of same day cancellations for planned treatment of atrial fibrillation with cardioversion for patients using the novel smartphone-based photoplethysmographic method for heart rhythm monitoring prior to the treatment compared to

					no monitoring [2 to 4 weeks].
Mobile Health Intervention for Rural Atrial Fibrillation [AFibLITT_R; NCT04076020] US	Status: Recruiting Estimated completion date: August 2023 Last update: January 2021	Interventional (randomised): n=264 2 study arms: - Relational agent and AliveCor Kardia use for 120 days - Usual care	Inclusion Criteria: Patients aged 18 years or older; Diagnosis of AF, identified from the EHR problem list and confirmed by 2 or more reports of AF from separate monitoring events at least 2 weeks apart (CG, Holter or event monitor); CHA2DS2-VASc of 2 or more; Prescribed use of warfarin or DOAC for AF stroke prevention; English-speaking well enough to participate in informed consent and this study; No plans to relocate from the area within 12 months of enrolment. Exclusion Criteria: Conditions other than AF that require anticoagulation; History of pulmonary vein isolation or foreseen pulmonary vein isolation; History of AV nodal ablation or foreseen AV nodal ablation; Heart failure necessitating hospital admission 3 months prior to study inclusion or less; Acute coronary syndrome 3 months or less prior to study inclusion; Untreated hyperthyroidism or, 3 months or less euthyroidism before inclusion; Foreseen pacemaker, internal cardioverter defibrillator, or cardiac resynchronization therapy; Cardiac surgery 3 months before inclusion or less; Planned cardiac surgery; Presence of non-cardiovascular	Medication possession ratio [12 months].	Self-reported adherence [4, 8 and 12 months]; Change from baseline AFEQT [4, 8 and 12 months]; Emergency room visits [4, 8 and 12 months]; Urgent care visits [4, 8 and 12 months]; Days of hospitalisation [4, 8 and 12 months].

			conditions likely to be fatal within 12 months; Inability to comprehend the study protocol.		
A Mobile Relational Agent to Enhance Atrial Fibrillation Self-Care [AFibLITT; NCT04075994] US	Status: Recruiting Estimated completion date: March 2024 Last update: January 2021	Interventional (randomised): n=240 2 arms: - Relational agent (smartphone-based intervention which simulates conversation) with usual care - Usual Care (brochure on AF, WebMD app and AliveCor Kardia heart rate and rhythm monitor)	Inclusion criteria: Age 21 years or older; patients with a diagnosis of AF, identified by EHR problem list and confirmed by 2 or more reports of AF from separate monitoring events at least 2 weeks apart; CHA2DS2-VASc of 2 or more; prescribed use of warfarin or DOAC for AF stroke prevention; English-speaking well enough to participate in informed consent and this study; no plans to relocate from the area within 12 months of enrolment. Exclusion criteria: Conditions other than AF that require anticoagulation; history of (or foreseen) pulmonary vein isolation; history of (or foreseen) AV nodal ablation; heart failure necessitating hospital admission months prior to study inclusion or less; acute coronary syndrome; untreated hyperthyroidism or, 3 months or less euthyroidism before inclusion; foreseen pacemaker, internal cardioverter defibrillator or cardiac resynchronization therapy; cardiac surgery 3 months before inclusion or less; planned cardiac surgery; presence of non-cardiovascular conditions likely to be fatal within 12 months; inability to comprehend the study protocol.	Medication possession ratio [12 months].	Self-reported adherence [Baseline, 4, 8 and 12 months]; Change from baseline AFEQT [Baseline, 4, 8 and 12 months]; emergency room visits [4, 8 and 12 months]; urgent care visits [4, 8 and 12 months]; days of hospitalization [4, 8 and 12 months].

Early Diagnosis of Atrial Fibrillation in the Wait-Time Prior to Seeing a Cardiologist [CATCH-AF; NCT04302311] Canada	Status: Recruiting Estimated completion date: July 2022 Last update: March 2020	Interventional (randomised): n=220 2 arms: - Standard of care (Holter monitoring) - Kardia AliveCor with additional Holter monitoring as needed	Inclusion Criteria: Patients aged 18 years or older; referral for episodic symptoms that may be due to arrhythmia (for example; palpitations, dyspnoea, or pre-syncope); At least one risk factor from CHADS-65 CCS Algorithm. Exclusion Criteria: Previous diagnosis of atrial fibrillation; already anticoagulated for another diagnosis (such as metallic heart valve or pulmonary embolism); symptoms typical of non-arrhythmic cause (such as exertional chest pain).	Time to atrial fibrillation diagnosis compared between arms as analysed by Kaplan-Meier survival curves [6 months].	Not provided.
Metformin as an Adjunctive Therapy to Catheter Ablation in Atrial Fibrillation [NCT04625946] US	Status: Recruiting Estimated completion date: November 2022 Last update: January 2021	Interventional (randomised): n=150 2 arms: - Standard of care with metformin - Standard of care (ablation with recommendations for lifestyle modification)	Inclusion criteria: Age 18 years or older; BMI greater than 25 with plan for rhythm control of AF by catheter ablation; able to understand and sign informed consent document. Exclusion criteria: Individuals with known diabetes; those already taking metformin or other antidiabetic medication including insulin; known allergy or FDA-labelled contradiction to taking metformin; patients taking carbonic anhydrase inhibitors, eGFR below 30ml/min or other clinical diagnosis of advanced renal disease; history of significant alcohol use; history of hepatic dysfunction; history of New York Heart Association Class III or IV heart failure; pregnancy or nursing.	Freedom from recurrent atrial arrhythmias by 6 months after a single ablation to eliminate AF.	Time to recurrence of AF after a 3 month blanking period of ablation; freedom from recurrent atrial arrhythmias at 1 year after ablation (after 3 month blanking period); freedom from recurrent atrial arrhythmias at 6 months after repeat ablation; AF severity score; percentage change in weight at 3 and 6 months after ablation; percentage change in haemoglobin A1c at 6 and 12 months after ablation; incidence of major procedural complications; AF related morbidity during follow-up; burden of AF assessed by AliveCor Kardia devices at 3 months, 6

					months and 12 months after ablation.
Better Outcomes for Anticoagulation Treatment Through Observation of Atrial Rhythm [BOAT OAR; NCT03515083] US	Status: Recruiting Estimated completion date: July 2022 Last update: March 2021	Interventional (randomised): n=100 2 arms: - Daily AliveCor Kardia ECG plus standard care - Standard care	Inclusion Criteria: Patients aged 18 years and older; Non-valvular atrial fibrillation that is either paroxysmal, persistent or permanent; CHA2DS2VASc score of 2 or more; Eligible for therapy with apixaban for at least 6 months; Possession of a smartphone capable of pairing with the AliveCor Kardia cardiac monitor. Exclusion Criteria: Contraindication to anticoagulation with apixaban for at least 6 months; No access to a smartphone capable of pairing with the AliveCor Kardia cardiac monitor; Unable to provide informed consent for this protocol.	Anticoagulation compliance [12 months].	Composite of deaths, strokes, and hospitalizations [12 months]; AF symptom severity [12 months].
A Fib Clinic of the Future Using KardiaPro Platform for Chronic Care of Patients With AF After Ablation Procedure [AliveCor study; NCT03557034] US	Status: Active, not recruiting Estimated completion date: December 2021 Last update: January 2021	Interventional (randomised): n=100 2 arms: - Standard of care monitoring - Kardia monitoring	Inclusion Criteria: 18 to 85 years old; Have smartphone with data plan; History of AF (paroxysmal or persistent); In sinus rhythm at the 3 to 4 month post-procedure visit and no evidence of AF during the interval starting after the 3 week blanking period and ending at the appointment time; On Anticoagulation if CHADS VASC score is 1 or higher and will continue to be on anticoagulation or CHADS VASC of Zero; Willing to follow-up with their Cleveland Clinic electrophysiologist in 6 months. Exclusion Criteria: Patients without smartphone; Unwilling to provide	Time to atrial fibrillation detection [6 months].	Incidence of atrial fibrillation after successful AF ablation [6 months]; Average number of atrial fibrillation episodes detected after successful ablation [6 months]; Average number of clinical encounters after successful ablation [6 months]; Use of alternative monitoring devices after successful ablation [6 months]; Change in level of anxiety from the date of AF ablation to the end of study period (measured using the Generalized Anxiety

			consent; Unwilling to follow-up in 6 months; CHADS VASC of 1 or more and anticoagulation will be stopped; Presence of a cardiac implantable electronic device; If the primary electrophysiologist decides the patient still needs monitoring through traditional monitors due to any reason.		Disorder 7-item scale (GAD-7) [6 months].
The Use of Prescribed Detraining to Decrease Atrial Fibrillation Burden and Symptoms in Athletes [DAF; NCT03642886] Canada	Status: Unknown Estimated completion date: April 2020 Last update: November 2018	Interventional (randomised): n=73 2 arms: - Continued strenuous athletics - Detraining period of 8-weeks	Inclusion criteria: Age 18 to 60; paroxysmal AF (subjects must have had more than 1 episode of AF within the last 12 months); performs prolonged regular sessions of strenuous practice (6 hours per week or more with intensity greater than 60% maximum heart rate for at least 6 months prior); preserved ejection fraction (55% or less) with an absence of structural heart disease. Exclusion criteria: BMI over 25 kg/m2; hypertension as per 2016 Canadian Hypertension Education Program Guidelines; diabetes; structural heart disease; obstructive sleep apnoea; metabolic abnormalities; pericarditis; coronary artery disease; pre-excitation, Brugada syndrome, long QT syndrome, arrhythmogenic cardiomyopathy or catecholamineregic polymorphic ventricular tachycardia; use of performance-enhancing agents; implanted cardiac pacemaker or	Ratio of AF episodes (the number of AF AliveCor transmissions over the total number of daily transmissions); the number of symptomatic palpitations that correspond with documented AF.	AF symptom severity score. AFEQT score; general quality of life; hospitalizations or emergency room visits; DC cardioversions; percentage of participants referred for AF ablation during the study; initiation of anti-arrhythmic drug therapy.

			defibrillator; a concurrent period of involuntary deconditioning.		
Cryoballoon vs. Rhythmia Guided Ablation for Recurrent Atrial Fibrillation Following Initial Cryoballoon Pulmonary Vein Isolation [NCT03811795] US	Status: Recruiting Estimated Completion Date: November 2022 Last update: March 2021	Interventional (randomised): n=50 2 arms: - Repeat cryoballoon ablation and ECG monitoring with Kardia Mobile - Radiofrequency ablation and ECG monitoring with Kardia Mobile	Inclusion Criteria: Individuals with paroxysmal or persistent AF undergoing repeat AF ablation as per recent HRS guidelines and standard practice; Individuals in whom the initial ablation approach was cryoballoon PVI at the enrolling institution more than 3 month or more prior to the anticipated repeat ablation; Age 18 years and above. Exclusion Criteria: Individuals with recurrent AF who previously underwent RF-based PVI; Individuals with known contraindications to ablation including permanent atrial fibrillation or intolerance of anticoagulation; Individuals unable or not willing to complete follow-up visits and examination for the duration of the study; Individuals without access to smartphone or tablet compatible with the monitoring system; Prior valve surgery or surgical AF ablation; Individuals with mental or physical limitations precluding informed consent; Individuals currently enrolled in another investigational study or registry; Women of childbearing potential who are, or plan to become, pregnant during the time of the study.	Freedom from atrial fibrillation [6 months].	Not provided.

Future Patient - Telerehabilitation of Atrial Fibrillation Patients [NCT04493437] Denmark	Status: Active, not recruiting Estimated completion date: December 2020 (no results posted) Last update: July 2020	Interventional (non-randomised): n=20 2 arms: - Telerehabilitation - Telerehabilitation and rehabilitation in healthcare centre.	Inclusion Criteria: Patients diagnosed with AF; Adults age 18 years and above; no upper age limit; Patients living in Skive and Viborg Municipality; Living at home and capable of caring for themself; Basic computer skills or a relative with basic computer skills. Exclusion Criteria: Pregnancy; Lack of ability to cooperate; Patient does not speak, read and understand Danish.	Clinical test of the contents of telerehabilitation programs using interviews [Day 30]; Usability test of technologies seen from patients' and healthcare professionals' perspectives [Day 30].	Measurements of blood pressure [Every Wednesday: week 1, 2, 3, 4, and 5]; Measurements of pulse [Every Wednesday: week 1, 2, 3, 4, and 5]; Measurements of weight [Every Wednesday: week 1, 2, 3, 4, and 5]; Measurements of electrocardiography (ECG) ECG QT Interval [Every Wednesday: week 1, 2, 3, 4, and 5]; Measurements of number of steps and sleep [Every Wednesday: week 1, 2, 3, 4, and 5]; Interviews on patients' and relatives' expectations for and experience with participation in the telerehabilitation program [Every Wednesday: week 1, 2, 3, 4, and 5].
Abbreviations: AF atrial fibrillation; AFEQT Atrial Fibrillation Effect on Quality of Life; AFL atrial flutter; AMI acute myocardial infarction; ASD atrial septal defect; CKD chronic kidney disease; ECG electrocardiogram; EP electrophysiology; HF heart failure; HRQoL health-related quality of life; ICD implantable cardioverter-defibrillator; IVC inferior vena cava; NYHA New York Heart Association; OAC oral anticoagulants; PAC; premature atrial complex; PoC point of care; PPG photoplethysmography; PVI pulmonary vein isolation; RCT randomised controlled trial; RF radiofrequency; SVT supraventricular tachycardia; TEE transoesophageal echocardiogram; TIA transient ischaemic attack; TTE transthoracic echocardiogram;					

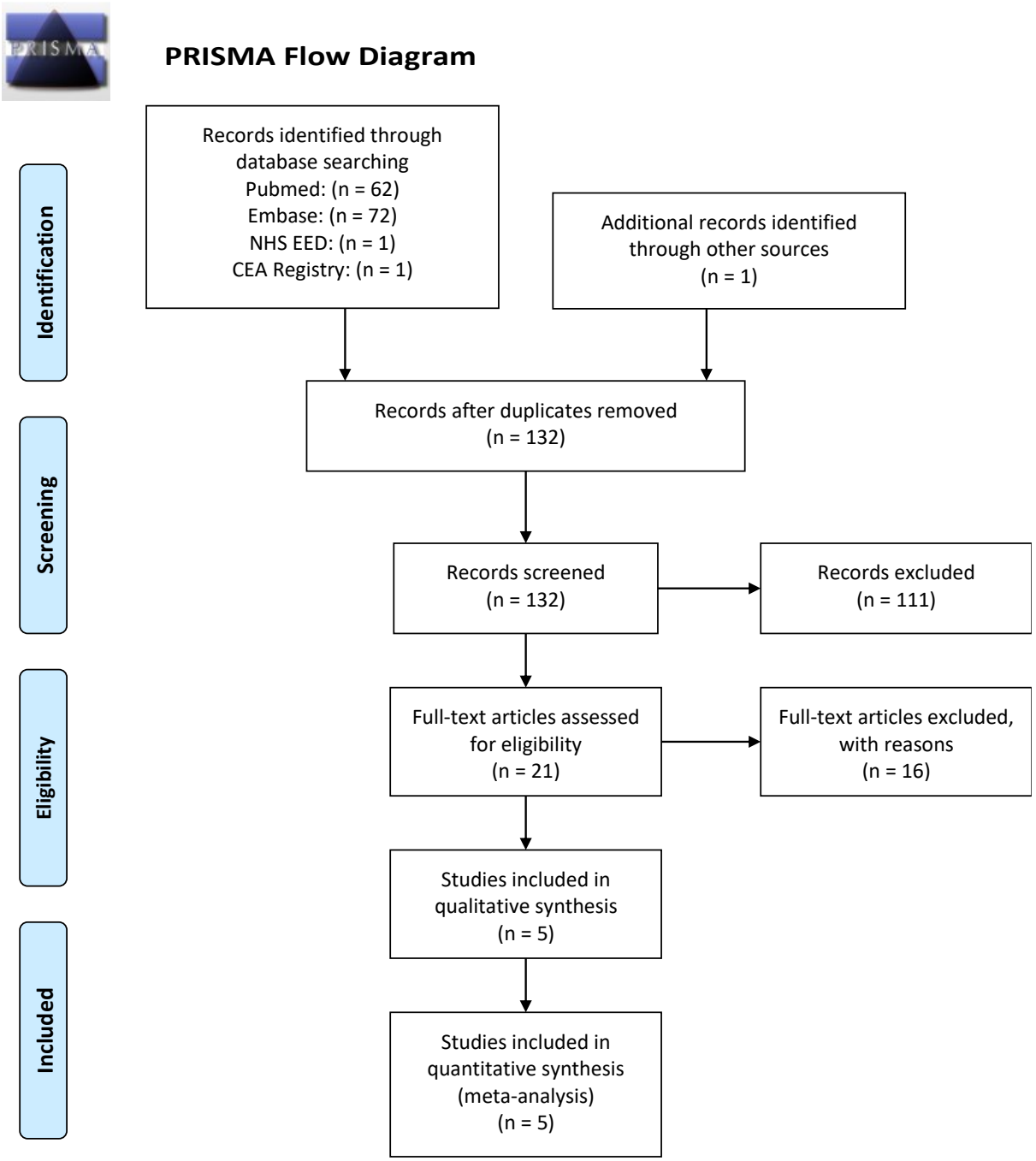
Appendix E: Economic literature search

Economic data search strategy, critique of company strategy.

Search Strategy (PubMed)	Database: PUBMED (All fields) <To 30th March, 2021>		Result
	1	**((((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR (non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)**	89,761
	2	**((((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro)**	20,214
	3	**#2 AND #3**	605
	4	**((((((((((((((((((economics/)) OR (value of life/)) OR (exp "costs and cost analysis"/)) OR (exp economics, hospital/)) OR (exp economics, medical/)) OR (exp resource allocation/)) OR (economics, nursing/)) OR (economics, pharmaceutical/)) OR (exp "fees and charges"/)) OR (exp budgets/)) OR (budget*.ti,ab.)) OR (cost*.ti,ab.)) OR ((economic* or pharmaco?economic*).ti,ab.)) OR ((price* or pricing*).ti,ab.)) OR ((financ* or fee or fees or expenditure* or saving*).ti,ab.)) OR ((value adj2 (money or monetary)).ti,ab.)) OR (resourc* allocat*.ti,ab.)) OR ((fund or funds or funding* or funded).ti,ab.)) OR ((ration or rations or rationing* or rationed).ti,ab.)**	1,878,757
	5	3 AND 4	62

Databases searched	• PubMed • Embase • NHS Economic Evaluation Database (NHS EED) • Database of Abstracts of Effects (DARE) • Health Technology Assessments (HTA) • Cost-effectiveness Analysis registry (CEA registry)

Company's PRISMA diagram of literature search and sift for clinical evidence [Appendix A of company Economic Submission]



Appendix F: Critical appraisal of economic evidence

Appendix F1: Published economic evidence

CHEERS Checklist: Praus *et al.* (2021)

First assessment: KK, QA: RO

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Partially	Economic study not mentioned in title or methods of abstract. Results of abstract include mention of cost saving. Title includes "personal electrocardiogram".
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	Partially	Structured abstract. Appears to be cost-calculator based on money saved of survey responders hypothetically attending emergency department or urgent care if they had not had access to KardiaMobile.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Yes	Scale of AF in US, and economic burden annually presented. "The purpose of this nurse practitioner (NP)-led quality improvement project was to improve patient outcomes, decrease resource utilization, and reduce anxiety related to AF through the use of a personal, single-lead electrocardiogram (ECG)."
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes	"Eligibility criteria included adult patients who (1) had two or more AF-related ED or UC visits in the past 12 months, (2) needed rate control with medication titration, or (3) needed monitoring for AF reoccurrence after reestablishing sinus rhythm—either by chemical or direct current cardioversion." No subgroups analysed.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	No	Setting reported as "cardiology division of a large multispecialty group, which is a subsidiary of a national health care organization", but not in the context of decision making. Not an economic model, is a cost calculator.

Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	No	Not reported
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	No	Not reported
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	No	Not reported
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A	Cost calculator
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	No	Not reported (for cost perspective)
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	No	Not reported
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Yes	"Participants completed two online surveys." "These questions address how the patient perceives access and communication with a cardiology provider, if unnecessary hospitalizations were avoided, and if anxiety levels were decreased. In addition, the surgery queried disposition – where the patient stated that they would have sought care – were the program not available. Options for disposition on the survey include an ED, UC, office visit or done nothing".
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions.	No	Not reported

		Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	No	Not reported (in Discussion it just states “using the previously calculated average for an ED visit”, assumed to be $7,450 from the Introduction, with no reference or method for estimation provided).
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A	Not a model, cost-calculator only
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods	N/A	

		for handling population heterogeneity and uncertainty.		
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	No	Costs only reported in the discussion section: "The actual number of avoided resource utilization is higher than the patient responses to the survey; however, if considering 11 patients who avoided an ED visit, this quality-improvement project realised a cost saving of $81,950, using the previously calculated average for an ED visit".
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	No	Not reported
Characterising uncertainty	20 a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	No	Not reported
	20 b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.		
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or	N/A	No subgroups analysed

		other observed variability in effects that are not reducible by more information.		
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes	Related to costs: “This is significantly under-estimated because potential hospitalizations and diverted UC visits are not included.” In Limitations, nothing specifically related to costs was stated.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes	“Competing interests: M. Proenza obtained funding from Southwest Medical, part of OptumCare for the KardiaMobile devices, and coordinated with Southwest Medical’s IT department.”
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes	As above.

CHEERS Checklist: Reed *et al.* (2019)

First assessment: KK, QA: RO

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Partially	Cost analysis not mentioned in title. Interventions compared are "Smartphone-based event recorder alongside standard care versus standard care"
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	Partially	Structured abstract. Emergency departments of 10 UK centres. Main study of clinical outcomes. RCT design. Economic methodology and outcomes not reported in abstract.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Yes	Palpitations and pre-syncope account for 1% of all ED visits (300,000 annually). "The primary aim of this study is to compare the symptomatic rhythm detection rate at 90 days of a smartphone-based event recorder (AliveCor) alongside standard care, compared to standard care alone, for participants presenting to the ED with palpitations and pre-syncope with no obvious cause evident initial consultation."
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes	"Participants aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythms during these episodes remains undiagnosed after ED assessment." No subgroups
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	No	Not an economic model, is a cost calculator.

Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes	"Overall and median healthcare utilisation costs (primary/community/secondary care and intervention costs) were calculated for both groups." NHS reference costs from 2016/17 used.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes	KardiaMobile and standard care versus standard care.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes	90 days
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A	Cost calculator
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes	Healthcare utilisation costs per symptomatic rhythm diagnosis.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	No	Cost calculator between two arms (cost-effectiveness not addressed)
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	No	Not reported
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost.	Yes	Costs calculated for each arm of RCT.

		Describe any adjustments made to approximate to opportunity costs.		
	13 b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes	NHS Reference costs 2016/17, with no adjustments used and no conversion needed.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A	Not an economic model, but cost-calculator in both arms.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	N/A	
Results				

Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	No	Not reported explicitly (but derived from NHS reference costs)
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes	Median, IQR and range of costs in intervention and control group both reported (p-value from Mann-Whitney analysis and cost difference per patient per symptomatic rhythm also reported). “Cost per symptomatic rhythm diagnosis was £921 less per patient per symptomatic rhythm in the intervention group (£474) compared to the control group (£1395).”
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	Not economic model
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.		
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A	No subgroups applied.
Discussion				

Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Partially	"Use of a smartphone-based event recorder increases the symptom-rhythm correlation rate over five-fold at 90 days with a reduced cost per diagnosis". "Whilst there was a potential variation in standard care between sites, this element of pragmatic design ensures our findings are generalisable across all types of standard care in the UK National Health Service without compromising validity." Limitations also reported.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes	"The study was funded by Chest, Heart and Stroke Scotland (Action Research Grant R15/A164; £23,056) and British Heart Foundation (BHF Project Grant no. PG/17/63/33198; £21,347) which included funding for purchasing the devices. MR was supported by an NHS Research Scotland Career Researcher Clinician award. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report."
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes	"The authors declare that they have no competing interests and no financial interest in the device used in this study. AliveCor had no involvement in the study"

CHEERS Checklist: YHEC (2018)
Items to include when reporting economic evaluations of health interventions

First assessment: KK, QA: RO

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Yes	"NHS Innovation Accelerator: Economic Impact Evaluation Case Study: AliveCor Kardia Mobile"
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	No	Not peer-reviewed publication, so no structured abstract.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Yes	"This case study focuses on the potential return on investment of replacing a 'typical AF diagnostic pathway' with a Kardia Mobile pathway, for the purposes of diagnosing AF. The analysis was developed in spring 2017 and was based on the information and evidence available at the time."
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	N/A	No patient recruitment.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	No	Not model
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes	NHS AF pathway.

Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	No	Not comparator – cost avoided (primary, secondary, diagnostic tests) analysis.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes	Year 1 (Table 4.1)
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	No	Not reported
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	N/A	Not modelled
Measurement of effectiveness	11 a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A	Cost avoided analysis
	11 b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	No	Not reported
Estimating resources and costs	13 a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	No comparator included
	13 b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate		

		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes	All references and dates provided (no currency conversion needed)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	No	Not reported (however not strictly a model, but cost calculator reporting avoidable healthcare utilization).
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	N/A	
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to	Partially	Table 4.1 shows financial impact of Kardia Mobile per patient investigated for AF. No distributions included, but section 4.1 details variations in inputs for sensitivity analysis.

		represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.		
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	No	Not reported
Characterising uncertainty	20 a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	No	Not reported
	20 b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.		
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A	No patients recruited
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes	"The analysis undertaken concludes that Kardia Mobile is a cost saving innovation, showing estimated net benefit of £968 per patient investigated and potential ROI from an NHS perspective of 666%, based on the assumptions stated. There are also intangible patient benefits of reduced anxiety and the potential for

				avoided cardiovascular events, which have not been costed in this analysis." Limitations also listed upfront in Background.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	No	Not explicitly reported
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	No	Although authored by YHEC (private consultancy firm).

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: https://www.ispor.org/heor-resources/good-practices/article/consolidated-health-economic-evaluation-reporting-standards-(cheers)---explanation-and-elaboration

Appendix F2: Critique of *de novo* model (Drummond checklist 1996)

First assessment: KK, QA: RO

Item	Judgement	EAC Comment
Study design		
1* The research question is stated.	Yes	"*Use of the KardiaMobile system (KardiaMobile hardware [single-lead or 6 lead ECG monitor] and KardiaMobile app) for the ambulatory detection of AF compared with (1) Holter monitoring (24h, 48h, and 7-day), and (2) use of the Zio patch electrode monitor (PEM) (14-day).*"
2* The economic importance of the research question is stated.	No	Implied however, as it is a submission to NICE.
3* The viewpoint(s) of the analysis are clearly stated and justified.	Yes	*"The model was developed from the perspective of the National Health Service (NHS) in England and Personal Social Services (PSS)"*
4* The rationale for choosing alternative programmes or interventions compared is stated.	No	Comparators listed as Holter (24h, 48, 7d) and Zio patch, however no rationale provided. Additionally, repeat monitoring costs include continuous event recorder and implantable cardiac devices without adequate justification.
5* The alternatives being compared are clearly described.	Not clear	Comparators listed in Economic Submission, however comparators need to be selected in the "RESULTS" worksheet of the model (not transparent and counterintuitive).
6* The form of economic evaluation used is stated.	Yes	Cost consequences (cost-effectiveness included; QALYs, ICERs)
7* The choice of form of economic evaluation is justified in relation to the questions addressed.	No	Model structure and complexity not adequately justified in Economic Submission.
Data collection		
8* The source(s) of effectiveness estimates used are stated.	Not clear	Some input parameters described in Economic Model do not match values used in *de novo* model.

Item		Judgement	EAC Comment
9	Details of the design and results of effectiveness study are given (if based on a single study).	Not applicable	
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Not applicable	
11*	The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Following diagnosis phase patients populate three following health states: AF with no complications, no AF, undiagnosed AF. During management phase patients can populate clinical event states: stroke, myocardial infarction, intracranial haemorrhage, major bleeding and death.
12	Methods to value benefits are stated.	Not clear	Utility values and sources not included in Economic Submission, however are described (with reference provided) in the *de novo* model.
13	Details of the subjects from whom valuations were obtained were given.	Not clear	Throughout Economic Submission “experts” were mentioned however only one named expert listed.
14	Productivity changes (if included) are reported separately.	Not applicable	
15	The relevance of productivity changes to the study question is discussed.	Not applicable	
16*	Quantities of resource use are reported separately from their unit costs.	Not clear	For KardiaMobile includes 10 minutes of nurse time to prepare device and train patients. Time and resource associated with ECG review were not included in the model or Economic Submission for intervention or comparators.
17*	Methods for the estimation of quantities and unit costs are described.	Not clear	Repeated monitoring advised by expert opinion only. Economic Submission and model provided references to costs, however EAC were unable to verify some values.
18*	Currency and price data are recorded.	Yes	Costs described (GBP)
19*	Details of currency of price adjustments for inflation or currency conversion are given.	No	A number of parameters have been inflated however the inflation is not transparently described.

Item		Judgement	EAC Comment
20	Details of any model used are given.	Yes	*"A Markov-cohort economic model was developed to capture the short- and long-term costs and health outcomes associated with monitoring for AF with KardiaMobile, and alternative technologies".* First stage includes diagnosis (max 100 days, daily cycle length), followed by management phase (5 years, 1 year cycle length).
21	The choice of model used and the key parameters on which it is based are justified.	Not clear	Clinical parameters described in Table 3 of submission, other parameters used in Table 4, costs in later section of Economic Submission. Some references provided. Some incorrect references were provided, and some values were calculated and not justified (in the model or the Economic Submission).
Analysis and interpretation of results			
22*	Time horizon of costs and benefits is stated.	Yes	100 day monitoring phase, followed by a 5 year management phase.
23	The discount rate(s) is stated.	Yes	*"Costs and health outcomes occurring beyond 1 year were discounted at a rate of 3.5% (6)."*
24	The choice of discount rate(s) is justified.	Yes	References to NICE Guide to the methods of technology appraisal 2013.
25	An explanation is given if costs and benefits are not discounted.	Not applicable	
26	Details of statistical tests and confidence intervals are given for stochastic data.	Not applicable	
27	The approach to sensitivity analysis is given.	Yes	*"Multiple sensitivity analyses were conducted to explore the impact of parameter variations on the model outputs. In the first analysis (multiple one-way sensitivity analyses), all model parameters were varied (increased and decreased) to explore the impact that this had on the incremental cost of the intervention (with results presented in the form of tornado diagrams)."*
28	The choice of variables for sensitivity analysis is justified.	Yes	All model parameters were varied (extensive approach). Tornado diagram provided.

Item		Judgement	EAC Comment
29	The ranges over which the variables are varied are justified.	Not clear	"*If available, the 95% confidence interval for that value was used to inform the variation, and where the confidence interval was unavailable clinical parameters were varied by 20% and cost parameters by 50%."* Varying some parameters by a fixed 20% or 50% may not include a plausible range.
30	Relevant alternatives are compared.	Not clear	As basecase includes 14 day duration of KardiaMobile monitoring, the relevance of implantable cardiac monitoring is unclear. Holter and CER appear relevant, however Zio was not included in the decision problem, and no direct comparison of Zio and KardiaMobile has been identified.
31	Incremental analysis is reported.	Yes	Tornado diagram provided (demonstrating incremental cost when varying 41 parameters)
32*	Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	Table 9 of Economic Submission reports base-case totals and breakdown of costs of primary monitoring, repeat monitoring, primary care visits (all £0 and not applied in model), secondary care visits, anticoagulants, stroke, major bleeding, intracranial haemorrhage, myocardial infarction, fatal events (stroke, major bleeding, intracranial haemorrhage, myocardial infarction), two events, three events, four events.
33*	The answer to the study question is given.	Yes	*"Base-case cost results from the model (Table 9) indicate that the technology is cost saving per patient when compared with all included comparators."*
34*	Conclusions follow from the data reported.	Yes	*"Following introduction of KardiaMobile, cost savings are largely driven by a reductuion[sic] in the number of health care service visits, and associated costs, related to ambulatory monitoring in the short-term. The model output also indicates that introduction of the intervention reduces the costs, and clinical event rate, associated with stroke and MI. These events are associated with high treatment and management costs. Thus, both short- and long-term health care cost savings are projected."*
35*	Conclusions are accompanied by the appropriate caveats.	Yes	3 limitations are listed. *"Limitations of this analysis were as follows:* • *There was a relative lack of large head-to-head comparisons of the KardiaMobile device with Zio patch.* • *Despite a well-designed study by Hermans et al. 2021 (9) being utilised in this analysis, the study is focused on the post-ablation population.*

Item	Judgement	EAC Comment
		Additionally, the source of clinical data for Zio patch (Kaura et al. 2019 (12)) is focused on the post-stroke population. • *Clinical expert input was relied upon to inform the probabilities of subsequent ambulatory monitoring and the switching pattern between different technologies, due to lack of data available to inform these model parameters.* *Despite the above limitations, the base-case analysis results, and the results of sensitivity analyses, indicated that the magnitude of demonstrated savings is sufficiently large to suggest that only major variations in input parameter values are likely to change the conclusions of the analysis."*
* Not justified is not considered an available option		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

KardiaMobile for detecting atrial fibrillation

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Results of patient survey
- [Appendix D: Decision problem

1 The technology

KardiaMobile (AliveCor) is a portable electrocardiogram (ECG) recorder. It works with a compatible mobile device, such as a smartphone or tablet, to run the Kardia app, which analyses the ECG recording. The device is small and is designed to be used anywhere.

KardiaMobile is available as a single-lead or as a 6-lead (KardiaMobile 6L) ECG recorder. The single-lead version has 2 electrodes on the top surface; 2 fingers are placed on each electrode. KardiaMobile 6L has 3 electrodes; 2 electrodes on the top surface and one on the bottom which is placed on the left leg. The app has an option for either single-lead or 6-lead ECG readings. People must keep their arms still and must keep touching the electrodes for at least 30 seconds for a complete reading to be taken. Healthcare professionals may advise on the frequency and length of use for detecting atrial fibrillation (AF).

While taking a reading, the ECG recoding is sent wirelessly to the mobile device, where it can be viewed using the Kardia app. Internet access is not needed when taking the reading. The app works on devices running Apple or Android operating systems (a full list is available on the compatibility section of the company's website). It shows the ECG trace, a measure of heart rate, and it uses an artificial intelligence led algorithm to classify the traces as:

- normal
- possible AF
- tachycardia
- bradycardia or
- unclassified.

ECG traces measured by the device can be sent from the Kardia app via smartphone or tablet by email as a PDF attachment to a healthcare professional. When the device has a Wi-Fi or mobile connection, the recording automatically synchronises with a secure encrypted cloud server (this can be turned off manually from the device). The KardiaPro software, is an additional

option for healthcare professionals, which allows remote monitoring of users and generation of reports.

KardiaMobile is not intended for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices. The company states that the ECG recorded by KardiaMobile is used to detect heart rhythm disturbances but is not intended to be used to diagnose other cardiac conditions. The device instructions for use state that all interpretations should be reviewed by a healthcare professional and used to support clinical decision-making.

The technology has previously been known as AliveCor Heart Monitor and AliveCor Mobile ECG.

2 Proposed use of the technology

2.1 Disease or condition

Atrial fibrillation is the most common sustained cardiac arrhythmia. It has been estimated that 1.4 million people in England have atrial fibrillation, equating to 2.5% of the population. People with atrial fibrillation may present with breathlessness, heart palpitations and dizziness or temporary loss of consciousness. The frequency and severity of symptoms varies from person to person and symptoms of a person can also fluctuate widely over time. These changes can be monitored via ECG.

Atrial fibrillation is associated with an increased risk of thrombo-embolic complications including stroke, as well as the need for hospitalisation, and death. Untreated atrial fibrillation is associated with an increased risk of stroke and heart failure (European Society of Cardiology, 2012).

2.2 Patient group

KardiaMobile is designed for use in adults to detect abnormal heart rhythms (cardiac arrhythmia) via single time point testing or longer term monitoring to support clinical decision-making. This guidance focuses on the use of

KardiaMobile for detecting atrial fibrillation in people referred for electrocardiogram (ECG) monitoring.

2.3 Current management

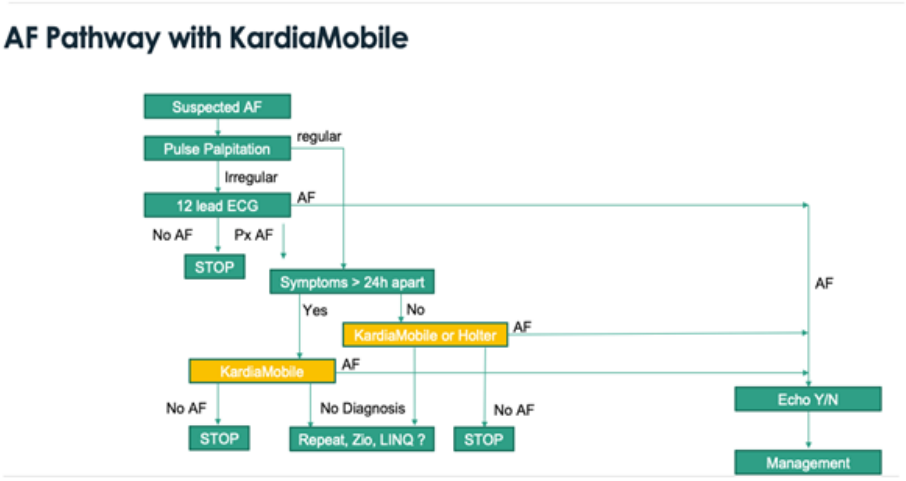
In clinical practice, an ECG is commonly used to diagnose an arrhythmia. An ECG is done in a general practice or hospital setting and records heart rhythm over a short period of time. If the ECG does not reveal an abnormality at the point of testing, the person's heart rhythm may need monitoring for a longer period of time. This may involve wearing a small portable ECG recording device for 24 hours or longer. This is often known as Holter monitor or ambulatory ECG monitoring. Alternatively, cardiac event recorders may be used in patients with occasional symptoms. These are either a portable device to record the heart rhythm at the time of symptoms using a device that is worn strapped to a person's body and may require electrodes to be stuck to the skin, or a device that is implanted under the skin.

NICE's guidelines on managing atrial fibrillation and transient loss of consciousness ('blackouts') in over 16s provide recommendations on current methods of arrhythmia detection.

2.4 Proposed management with new technology

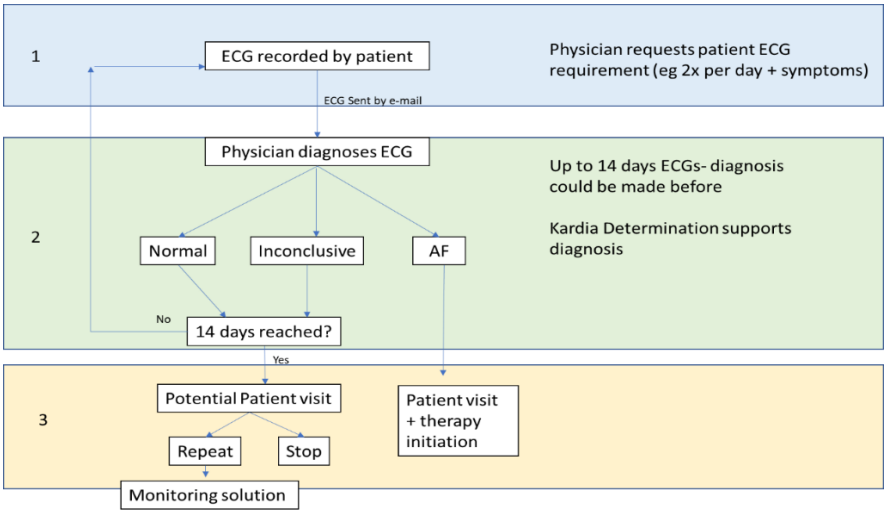
The company proposes that KardiaMobile replaces external event recorders and may be used alongside continuous ambulatory monitoring (for example, Holter) in adult symptomatic patients (see the figure 1).

Figure 1: Company proposed AF pathway using KardiaMobile



The use of KardiaMobile would be prescribed by a clinician and frequency of use is likely to depend on population; for example people with palpitations may be told to record ECG when symptomatic, whereas following a stroke, people may be advised to record an ECG up to 4 times a day. The clinical experts also stated duration of use would vary depending on the population, of between 14 and 90 days. The company also confirmed that the clinician would advise the person on which results were to be emailed for clinical review. The company also provided a proposed workflow using of KardiaMobile in NHS setting (see figure 2).

Figure 2: Workflow of KardiaMobile in NHS setting



The EAC considers that the proposed workflow (described above) is dependent upon the person emailing the ECG recording. This proposed

process could introduce bias through missing data (for example the person may forget to send email), and the security of the approach should be considered (as the ECG trace contains patient identifiers and is emailed from the patient's personal email as an attachment).

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem are described in Appendix D:

The only variation to the scope proposed by the company was the inclusion of outcomes reported in the included clinical studies only.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified a total of 24 peer-reviewed studies and 9 conference abstracts from a systematic search.

The EAC included 16 of the publications described in the company submission. The EAC identified 2 more recent studies which supersede those submitted by the company: an RCT by Guhl et al. 2020 (which supersedes the Magnani et al. 2017 pilot study), and RCT by Koh et al. 2021 (which supersedes the Koh et al. 2019 abstract). The EAC identified an additional 4 peer-reviewed publications and 10 conference abstracts not included in the company submission. Therefore, a total of 32 publications on 27 studies were considered by the EAC to be relevant including the iHeart study of the 5 publications and 2 abstracts (Ross et al. 2016, Smith et al 2016) had the same population but different outcomes reported). Table 1 presents the publications of the studies included in the company submission and EAC assessment.

Table 1: Publications of the studies in the company submission and the assessment report.

Studies included by both EAC and company	
Publication and study design	16 publications on 15 studies: • 2 RCTs (Reed et al. 2019; Goldenthal et al. 2019[iHeart]) • 4 diagnostic studies (Hermans et al. 2021; Narasimha et al. 2018; Selder et al. 2019; William et al. 2018) • 5 single-arm studies (Praus et al. 2021; Reed et al. 2021; Lowres et al. 2020; Yan et al. 2020; Lowres et al. 2016) • 1 case control study (Hickey et al. 2017) • 4 abstracts (Javed et al. 2019; Reading et al 2017[iHeart]; Philip et al. 2016; Goel et al. 2018)
Studies in company submission excluded by EAC	
Publication and study design	15 publication on 15 studies submitted by the company were excluded by the EAC: • 3 RCTs were excluded because of screening population, mixed interventions and the relevance of outcomes reported (Treskes et al. 2020; Bhavnani et al. 2018; Halcox et al. 2017) • 5 diagnostic studies (Karregat et al. 2021; Wasserlauf et al. 2019; Rajakariar et al. 2018; Haberman et al. 2015; Tarakji et al. 2015) were excluded because of single-time point detecting KardiaBand, comparator not in the NHS) • 3 cohort studies (Selder et al. 2020; Soni et al. 2019; Soni et al. 2016) were excluded because of the intervention as KardiaBand and screening population. • 4 abstracts (Dankers et al. 2019; Grieten et al. 2017; Bose et al. 2014; Saxon et al. 2012) were excluded because of population, intervention as KardiaBand and insufficient data on population.
Publications not in company submission included by EAC	
Publication and study design	16 publications including 14 additional publications on 10 studies plus 2 updates were included by the EAC: • 3 RCTs (Koh et al. 2021 which supersedes the Koh et al. 2019 conference abstract; Guhl et al. 2020 supersedes the Magnani et al. 2017 pilot study; Caceres et al. 2020[iHeart]) • 2 cohort studies (Bray et al. 2021; Dimarco et al. 2018) • 1 case report (Hickey et al. 2013) • 10 abstracts (Frey et al. 2020; Gupta et al. 2020; Scales et al. 2020; Lambert et al. 2019; Turchioe et al. 2019[iHeart]; Reading et al. 2018[iHeart]; Carlson et al. 2016; Onwordi et al. 2016; Ross et al. 2016; Smith et al. 2016)

There are 5 peer reviewed publications on 4 RCTs including Caceres et al. 2020 and Goldenthal et al. 2019 that reported different outcomes of the iHeart trial. The EAC considered that all 4 RCTs were moderate quality. The study participants and the ECG interpreter were not blinded to use of the KardiaMobile device or its output, and this risked performance and detection bias, although the EAC recognises that this lack of blinding is unavoidable. One trial was done in a UK NHS setting (Reed et al. 2019).

Three peer reviewed diagnostic studies (Hermans et al. 2021, Narasimha et al 2018 and William et al. 2018) were considered to have selection bias due to the study population. Narasimha et al (2018) was also considered to have an additional risk of bias because not all people were included in the analysis (5/38. 13% were excluded) and patient compliance influenced the results. Selder et al. (2019) was the largest diagnostic accuracy study (n=233) but patient selection was at the discretion of the physician, therefore included a mixed population.

Of 7 single-arm observational studies, population size ranged from 29 (Lowres et al. 2020) to 1,079 (Yan et al. 2020), including people presenting with palpitations, people with AF, or people with new onset AF after surgical procedures. Three studies were in a UK setting across primary care and secondary care (Bray et al. 2021; Reed et al. 2021; Dimarco et al. 2018). Study follow ups were from 4 weeks to 16 months.

The case control study (Hickey et al. 2017) had a small sample size of people using KardiaMobile once daily or when symptomatic (n=23), and they received additional educational messages which may have influenced their behaviour (and potentially study outcomes) and could limit generalisability. The study reported an aggregated outcome, combining detection of AF and atrial flutter. People were followed for 6 months, and Kaplan-Meier analysis was conducted.

One case report of a single patient and the 14 publications on 12 studies available in abstract form were not critically appraised. They were included in the assessment due to their value in demonstrating longitudinal use, device acceptability and ease of use.

Results from the peer-reviewed studies are presented in Table 2 (see below) and summarised as following:

- Diagnostic accuracy was reported in 5 studies including 1 abstract. One study (William et al. 2018) reported Kardia algorithm classification had 96.6% sensitivity and 94.1% specificity for detecting AF compared with a

12-lead ECG. When compared with clinical interpretation of the KardiaMobile ECG, Kardia algorithm had a sensitivity ranging between 92% and 99% per ECG recording, with a specificity between 92% and 98%.

- Diagnostic yield (the percentage of people with atrial fibrillation detected) was reported in 6 comparative studies. Three RCTs showed that significantly more people in the KardiaMobile ECG monitor group had cardiac arrhythmia detected compared with those in the control group (standard care, which included 24-hour Holter monitoring). This was supported by the results from an observational study (Yan et al. 2020).
- Patient experience using KardiaMobile was also reported in 12 studies. KardiaMobile device was thought to be easier to use compared with other ECG monitors such as Holter monitor. People found the KardiaMobile device accessible at symptom onset. People were generally satisfied with the device and felt that KardiaMobile would be useful in self-monitoring at home with an improvement in their ability to access to care they needed.
- Quality of life was reported in 5 studies including 1 abstract. Two RCTs and 1 abstract measured AF specific quality of life used AFEQT (a validated 20-item instrument measuring self-reported health related quality of life specific to AF). Two trials showed people used the KardiaMobile device had a significant improvement in AFEQT scores compared with those in the control groups.
- Clinical outcomes such as mortality, hospital use, and time to AF detection or treatment were also reported.
  - Only 1 death was reported in an RCT (Reed et al. 2019). This trial also showed that significantly more emergency department attendances due to palpitations or pre-syncope in people used KardiaMobile in addition to standard care than those had standard care alone (9.7% versus 2.6%). But there was no significant difference in hospital admissions, emergency visits, outpatient appointments and GP attendances (Goldenthal et al. 2019, Reed et al. 2019, Hickey et al. 2017).
  - People using KardiaMobile had their symptomatic cardiac arrhythmia detected earlier than those receiving standard care (9.9 days versus

48.0 days, Reed et al. 2019). Goldenthal et al. (2019) reported a shorter time between detection and treatment in the control group than the KardiaMobile group (hazard ratio 0.33 [95% 0.57 to 2.92]).

- The percentage of unreadable ECG recordings ranged from 0.6% to 1.9% by the KardiaMobile device. The unreadable ECG occurs when an ECG trace has interference and cannot be interpreted by the Kardia app. A proportion of these can be interpreted by a clinician. The Kardia app has a classification of unclassified ECG, which refers to a ECG trace is interpretable (that is, has no interference) but does not fit the current algorithm classifications. The percentage of unclassified ECG recordings ranged from 9.6% to 27.6% in the studies. Software updates have reduced the proportion of unclassified recordings over time.

In summary, the results of the RCT and real-world studies showed an increased and earlier diagnostic yield AF detection with KardiaMobile when compared with standard care, which included Holter monitoring and event recorders. The sensitivity and specificity of the Kardia app in detecting AF and AF recurrence, on a per-ECG recording basis, is high when compared with clinical interpretation of the KardiaMobile ECG trace. Evidence on clinical outcomes is limited. The real-world evidence also reported high patient compliance due to the ease of use, with potential benefits in increased quality of life. Therefore, the EAC considered that the clinical evidence demonstrated that KardiaMobile could be an option for detecting AF.

However, the included studies were heterogeneous, conducted in different subgroups of people (with different underlying prevalence of AF), who were recruited in different settings, with different comparators and different reference standards. The clinical experts noted that a range of diagnostic monitoring tools are used for a variety of durations dependent on the patient characteristics, history, frequency and severity (with syncope being the most severe) of symptoms. The EAC concluded that overall, the evidence base was supportive of KardiaMobile being a safe and clinically effective tool to aid AF detection in people who need ambulatory ECG monitoring.

Table 2: Details of the peer-reviewed studies included in the assessment report.

Study, design location	Participants/ Population, follow-up	Intervention & comparator	Outcome measures and results	EAC Comments
Randomised controlled trial (no. of studies =4 had 5 publications)				
RCT (People with AF)				
Guhl et al. (2020), a single-centre parallel arm pilot trial. US	People aged ≥18 years with a history of chronic AF who were prescribed oral anticoagulation for stroke prevention secondary to AF, and speak English-speaking sufficient to use a smartphone (n=120). Follow up: 30 days	intervention: Kardia device and app. Plus a smartphone-based relational agent. (n=59) control: usual care (not described in the study) (n=61)	Quality of life • AFEQT is a validated 20-item instrument measuring self-reported HRQoL specific to AF. (range 0-100, higher scores associated with superior HRQoL). Intervention participants had better scores in total AFEQT (adjusted mean difference 4.5; 95% CI 0.6-8.3; P=.03) and daily activity domain (adjusted mean difference 7.1; 95% CI 1.8-12.4; P=.009) scores compared with the control when adjusted scores at baseline. Adherence of anticoagulation • There was significantly greater improvement in the interventional group compared with the control group for both self-report anticoagulant adherence items. Acceptability • People found the relational agent useful, informative, and trustworthy.	Subsequent to pilot published by Magnani et al. 2017 (which was identified by the company). Mixed intervention, assessment of AF burden
Caceres et al. (2020) (iHeart), single-centre, US	People aged 18 years with documented AF who were undergoing treatment for their AF with either direct current cardioversion or radiofrequency ablation to restore normal sinus rhythm. Follow-up: 6 months	Intervention: In addition to usual care, people received the iHEART intervention received an iPhone that was equipped with the AliveCor Kardia mobile ECG system and unlimited data/text messaging (n=115) Control: People in the usual care group received guideline directed medical care defined by the treating cardiologist and evidence-based clinical guidelines for the management of AF. (n=123)	HRQOL • People in intervention group had higher scores for all Atrial Fibrillation Effect on Quality of Life subscales (including symptoms, daily activities, treatment concern, and satisfaction), • People in control group demonstrated changes only in the symptoms and daily activities subscales. • People in intervention group had improved scores on the physical component summary of the Short-Form Health Survey (mean change, 3.0; P < .05). • The EuroQol-5D score was unchanged. Scores on the Atrial Fibrillation Severity Scale significantly decreased, 5.4 and 4.5 points for the intervention and control groups, respectively. There was no difference in the EuroQol-5D scores between the intervention and control group. • The global Atrial Fibrillation Effect on Quality of Life score and all subscales had greater improvement in the intervention	

			group than in the control group, these differences did not reach statistical significance.	
Goldenthal *et al.* 2019, (iHeart) single-cetnre US.	People aged 18 and older with a history of documented AF and at least one AF risk factor (sedentary lifestyle, obesity, hypertension, smoking, and diabetes). Follow-up: 6 months	Intervention: received an iPhone and cellular service plan with unlimited data/text messaging, and the KardiaMobile ECG monitor. People were instructed to record a daily ECG and additional ECGs whenever they experienced symptoms perceived to be associated with an atrial arrhythmia (n=115) Control: usual cardiac care (not defined in the study) (n=123)	Detection • AF and AFL: the likelihood of recurrence AF and AFL detection was significantly greater in the intervention group (hazard ratio = 1.56, 95% CI: 1.06-2.30, P = 0.024). • Arrhythmia: while there was greater arrhythmia detection in the intervention group, the difference was not significant when only late recurrences (post 1 month) are considered. (hazard ratio = 1.29, 95% CI: 0.57-2.92, P = 0.54). People with recurrent AF/AFL in the intervention group were less likely to be treated than those in the control group (hazard ratio = 0.33, 95% CI: 0.57-2.92, P < .0001). The majority of patients did not use the KardiaMobile device to report their symptoms: only 11 (10%) patients transmitted symptom data along with their ECGs. Ten of these patients reported experiencing AF symptoms when the associated ECG revealed sinus rhythm. Hospital usage People in the control group had a higher number of all-cause hospitalizations (56) and emergency room visits (13) than the intervention group (45 hospitalizations and three emergency room visits). However, this difference is not statistically significant.	Composite outcome (AF and flutter). Recurrence defined as KardiaMobile output or ECG in patients' electronic health record
RCT (people with palpitation)				
Reed *et al.* 2019, 10 centres open label, randomised controlled trial. UK. Between 4 July 2016 and 9 January 2018. Funding: This study was funded by research awards from Chest, Heart and Stroke Scotland (CHSS) and British Heart Foundation (BHF) which included funding for	People aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythm during these episodes remains undiagnosed after emergency department assessment. Follow-up: 90 days	Intervention: standard care plus the use of a smartphone-based event recorder. (n=124 available for analysis). Control: standard care (participants received no other intervention) (n=116).	Detection rate • A symptomatic rhythm was detected in 55.6% (n=69) people in the intervention group versus 9.5% (n=11). Relative rate (RR)= 5.9, 95% CI 3.3–10.5; p < 0.0001. • A symptomatic cardiac arrhythmia was detected in 8.9% (n=11) people including 8 people with AF and 1 with AF flutter in the intervention group versus 0.9% (n=1) in the control group (no AF or AF flutter was detected). RR 10.3, 95% CI 1.3–78.5; p = 0.006). Mean time to symptomatic rhythm detection • 9.5 days, SD 16.1 (intervention) versus 42.9 days, SD 16.0 (control). P<0.0001. Mean time to symptomatic cardiac arrhythmia detection • 9.9 days, SD 15.6 (intervention) versus 48.0 days SD (control, 1 person). P=0.0004.	Contains patients aged less than 18 years.

purchasing the devices. MR was supported by an NHS Research Scotland Career Researcher Clinician award.			At 90 days, no. of people underwent for planned treatment: n=12 (intervention) versus n=6 (control group) (p = 0.192). ED presentations • 9.7%, n=12 (intervention) versus 2.6% (n=3) p = 0.031. Mortality: n=1 (intervention) versus n=0 (control). Hospital use • There were more ED presentations (after index visit) due to palpitations/pre-syncope in the intervention group (12/124; 9.7%; 95% CI 4.5–14.9% with 1 or more non index ED presentations) compared to the control group (3/116; 2.6%; 95% CI 0.0–5.5%; p = 0.031) • There was no difference in the number of inpatient hospital days due to palpitations or pre-syncope in the intervention group, the number of outpatient presentations due to palpitations or pre-syncope, number of GP presentations due to palpitations or pre-syncope or number of ECGs performed due to palpitations or pre-syncope.	
RCT (people at risk of AF)				
Koh *et al.* 2021 a multicentre, open-label study. Malaysia	People aged ≥55 years old, without known AF, with a recent ischaemic stroke or transient ischaemic attack (TIA) within the preceding 12 months. Follow up: 30 days ECG monitoring	Intervention: KardiaMobile (n=105) Comparator: 24-h Holter monitoring (n=98)	AF detection rate AF lasting ≥30 s was detected in 10 of 105 patients in the intervention group and 2 of 98 patients in the control group (9.5% vs. 2.0%; absolute difference 7.5%; P = 0.024). Medication use After the 30-day smartphone monitoring, there was a significantly higher proportion of patients on oral anticoagulation therapy at 3 months compared with baseline in the intervention group (9.5% vs. 0%, P = 0.002).	Published after clinical submission by company, supersedes abstract identified by the company
Diagnostic study (cross sectional) (no. of studies=4)				
Diagnostic study (people with AF)				
Hermans *et al.* 2021	Patients aged 18 years or older undergoing AF ablation, who had a smartphone and were able to operate KardiaMobile-1L (n=115) Follow-up: 4 weeks	Intervention: AliveCor Kardia heart rhythm monitoring (ACK) Comparator: continuous (Holter) heart rhythm monitoring.	Diagnostic accuracy • Sensitivity and specificity of ACK for AF detection were 95.3% and 97.5%. AFAF recurrent detection rate • ACK detected 29 (25.2%) people with AF recurrences versus 17 (14.8%) by Holter monitoring (p < 0.001). Easy to use	Holter monitor and KardiaMobile used at different time points across cohort.

			• People graded ACK higher than Holter monitoring and found ACK more convenient in daily usage than Holter ($p < 0.001$).	
William et al. 2018, single centre study, US	People aged 35–85 years with a history of paroxysmal or persistent AF, with baseline corrected QT interval less than 470 or 500 ms if the QRS duration was greater than 120ms.(n=52)	People were provided with a KMCMpaired with an iPod at the time of their admission for antiarrhythmic drug initiation. Dofetilide or sotalol were administered twice daily for 6 monitored doses during admission, with 12-lead ECG recordings performed 2 hours after each dose. People were instructed to perform a 30-second recording using a lead I ECG monitor immediately after each 12-lead ECG recording.	Diagnostic accuracy: • Kardia algorithm interpretation had 96.6% sensitivity and 94.1% specificity for the detection of AF as compared with physician-interpreted 12-lead ECGs. (based on 161 interpretable recordings). Of the 225 simultaneous recordings, 28.8% of ECG-determined AF was not detected by the KMCM algorithm; 91.3% of these were due to "unclassified" recordings by the Kardia algorithm. • Physician interpretation of the Kardia recording had 100% sensitivity and 89.2% specificity for the detection of AF as compared with physician-interpreted 12-lead ECGs (based on 214 recordings) • KMCM automated algorithm interpretation had 92.4% sensitivity and 97.8% specificity for the detection of AF as compared with physician-interpreted KMCM recordings (based on 159 recordings). • Of the 57 algorithm "unclassified" KMCM recordings, physician KMCM recording interpretation had 100% sensitivity and 79.5% specificity for the detection of AF as compared with 12-lead ECG interpretation. Easy to use The majority of people (93.6%) found the KMCM easy to use, and 59.6% noted that the use of the KMCM subjectively lessened AF diagnosis–related anxiety.	None
Diagnostic study (people with palpitations)				
Narasimha *et al.* 2018 US	People aged 18 years or over with palpitations (usually occurring less frequently than once a day) with prior nondiagnostic ECGs and/or Holter monitoring who demonstrated the ability to use a smartphone device to record and upload a test ECG recording at the office visit (n=33 with complete data)	People received KardiaMobile (KM) heart monitor and external loop recorder ELR (reference standard). People were asked to record a 30–60-second rhythm strip twice daily, regardless of symptoms, with KM device. The ECG recordings were received daily. The recording period varied from 14 to 30 days.	Diagnostic yield (percentage of patients with detected symptomatic or asymptomatic arrhythmias) Number of people identify with specific symptomatic arrhythmias by device ITT sample (n=38) KM: Atrial fibrillation 6 (15.8%); Aflutter 0; Any arrhythmia 34 (89.5%) ELR: Atrial fibrillation 4 (10.5%); Aflutter 2 (5.3%); Any arrhythmia 26 (68.4%)	Software not used for diagnosis.

		People who did not have a smartphone at the time of the study were provided with one free of charge for the duration of the study. KM was provided by the company free of charge.	The KM device had a total of 1,230 recorded tracings (roughly 30–35 tracings/patient). 563 were sinus rhythm and 667 abnormal rhythm tracings. There were a total of 1,121 tracings recorded by the ELR, with 520 normal sinus rhythm and 601 abnormal rhythm tracings. Time to rhythm detection: 266 days (KM) versus 161 (ELR). Easy to use: people reported that the KM was significantly easier to use than the ELR (1.4 vs 2.7; P < 0.01). The majority of the patients (87.1%) found the KM device "very accessible" at symptom onset. Compliance (percentage of days that the patient had at least one recording during the monitoring period) was significantly greater for the KM (91.2%) than for the ELR (52.7%, P < 0.01).	
Diagnostic study (mixed population)				
Selder *et al.* 2019 Netherlands	People presenting with paroxysmal AF, palpitations of unknown origin or near-collapse. (n=226 included in the analysis) Follow-up: between January 2017 and March 2018.	People received the KM device at home, downloaded the Kardia smartphone application. Whenever people experienced palpitations or related complaints, they were encouraged to record an ECG with the KM device. Reference test: ECG assessed by the Hartwacht team, consisting of a supervising cardiologist, a specialized cardiology nurse and a doctor's assistant.	Diagnostic accuracy During the study period 5,982 KM ECGs were received. • Using the assessment of the Hartwacht team as reference standard, the sensitivity of KM ECGs for detecting AF was 92% with a specificity of 95%. Detection rate • the KM algorithm categorised 3,548 (59%) as normal sinus rhythm, 1,301 (22%) as possible atrial fibrillation, 1,033 (17%) as unclassified and 100 (2%) as unreadable. Classification of the ECGs by the KM algorithm and diagnosis of the Hartwacht team differed significantly.	Potential inclusion of mixed population (have included people who may not have had AF or palpitations due to "discretion of physician.
Single-arm study (no. of studies=7)				
Single-arm study (people with AF)				
Praus *et al.* 2021 US	Adult who had 2 or more AF-related ED or UC visits in the past 12 months, needed rate control with medication titration, or needed monitoring for AF reoccurrence after reestablishing sinus rhythm—either by chemical or direct current cardioversion. (n=43)	A KardiaMobile (KM) device. People instructed to send daily readings and whenever symptomatic. If there is an abnormal result attempts were made to contact the person within an hour of ECG review, by telephone or	Detection rate A total of 1,501 ECG recordings were received and reviewed. Results of the KM device instant rhythm analysis revealed that 537 were interpreted as possible AF. There were 173 unclassified interpretations, 46 bradycardic, 24 tachycardic, 8 deemed uncategorized (due to artifact), and 3 recordings were too short to be interpreted. Medication use	Mixed intervention, single-arm

	Follow-up: 8 weeks	email; once contact was made, the patient was offered a NowClinic visit, although most were comfortable with telephone follow-up	Of the 43 patients, 17 required medication titrations for rate control, symptom control, or both. Of interest 3 of the 17 patients were thought to have been rate controlled. User experience The patient experience and satisfaction surveys were completed by 33 people (response rate of 77%). The majority of patients gave top ratings for the program's ability to decrease anxiety level (62% rated 5), provide empowerment to manage health concerns (72% rated), and increase ability to communicate with a provider and health care team (84% rated 5). People were highly satisfied with 90% of them giving a rating of 5 when asked how likely they were to recommend the KM device to other people with AF. Had the respondents not been in the study, 34% (n=11) indicated that they would have presented to an Emergency department (ED) and 25% would have presented to an urgent care (UC).	
Single-arm study (people at risk AF)				
Yan *et al.* 2020, a pragmatic observational, multi-centre study. Australia, China and Hong Kong	People presented with ischemic stroke or TIA with no known AF, and no AF on the admission 12-lead ECG. (n=1,079)	The AliveCor Kardia ECG monitor. People underwent intermittent hand-held iECG recordings that were performed by nursing staff trained to use the device on patients during routine nursing vital sign observations (typically every 2 to 4 hours) at the participating stroke units, until discharge. All people received in-patient 12-lead ECG. Patients also underwent in-patient or out-patient. Holter monitoring at the discretion of the treating stoke team, according to their usual practice.	Detecting rate (294 Had Holter monitoring and nurse-led iECG monitoring, and were included in primary analysis) • The nurse-led iECG recordings detected AF in 25 (8.5%) patients, while 24-hour Holter monitoring detected AF in eight (2.8%). (p<0.001) Time to detect AF • AF was detected significantly earlier by iECG recordings, at a median of 3 days from stroke onset (IQR, 2 to 6) than for the eight patients who had AF detected by Holter monitoring, in whom AF was detected at a median of 7 days after stroke (IQR, 6 to 10; P=0.02). For the 785 people who underwent iECG recording only, AF was detected in 69 (8.8%). The AF detection rate did not differ from those who had both iECG and 24-hour Holter monitoring (8.5%, P=0.8). The median days monitored from stroke onset to AF detection was 4 days for the subset who underwent iECG recordings only (IQR, 2 to 6), which did not differ from those who had both iECG and Holter recordings (3 days; IQR, 2 to 6; P=0.7).	Single-arm; included in adverse events only.
Lowres *et al.* 2020 , a prospective cross	People aged 18 years or over who had an episode of new-onset AF secondary to hospitalisation for either non-	Each person was provided with an AliveCor KardiaMobile ECG and Huawei Y560 smartphone.	Atrial fibrillation recurrence detection • 12/29 people were diagnosed with 'possible AF' by the device algorithm.	Single-arm; EAC only considered the adverse

sectional study, 3 hospitals Australia	cardiac surgery or non-cardiovascular acute medical illness (n=29 completed the intervention). Follow-up: 4 weeks (ECG recording)	They were asked to record their own ECG 3-times each day, for 4-weeks after hospital discharge.	• 10 of the 12 participants followed instructions and sought medical review prior to the 4-week follow-up, and all were confirmed with AF recurrence incidence 34% (95% CI, 18%-54%) (10/29). Time to defect AF AF recurrence was first identified at a median of 6 days (range 2–23 days) post discharge with 9/10 recurrences occurring in 9 days or less. Easy to use All 16 reported the ECG device was easy to use, and time taken to record ECGs was not onerous. The majority (11/16) also reported a sense of security from being able to self-monitor at home, reporting it was ‘‘reassuring” and gave them ‘‘a sense of control	events results from this study'
Lowres *et al.* 2016 cross-sectional study, Australia AliveCor provided ECG Heart Monitors for study	People aged 18 years or over who had cardiothoracic surgery and experienced a transient episode of postoperative atrial fibrillation (POAF) following cardiac surgery; with no history of AF prior to admission; who reverted or were cardioverted to stable sinus rhythm prior to discharge. (n=42) Follow-up: 4 weeks	People were provided with an iPhone and an AliveCor Heart monitor (iECG). People were requested to record a 30-s iECG 4 times a day during the study period, and take additional iECGs if AF symptoms were experienced, recording any symptoms in a diary.	Diagnostic accuracy • A total of 3481 iECGs were recorded and 3481 iECGs were recorded, of which 146 (4%) were non-diagnostic. • Of diagnostic 3335 records, the automated algorithm had sensitivity of 94.6% (95% CI, 85.1–98.9) and specificity 92.9% (95% CI, 92.0– 93.8) for detecting AF. AF recurrent detection • iECG detected recurrences of AF recurrence in 10/42 people. Easy to use • 95% of participants thought the device easy to use. Age was not a barrier using the device. Compliance • iECGs were recorded for a mean of 29 ± 5 days (range 9– 46), with 86% of participants recording iECGs for 27 days or more, and only 2 participants (5%) recording for <21 days. A mean of 2.8 ± 0.9 iECGs were recorded per day.	Interpretation by cardiologist included 12-lead ECG and Holter where available.
Single-arm study (people with palpitations)				
Reed *et al.* 2021, UK	People aged between 18 and 80 years presenting to the ED or Acute Medicine Unit (AMU) with palpitations or pre-syncope, whose ECG was normal, who had a compatible Apple/android phone, tablet, or watch, and in whom an underlying cardiac dysrhythmia was possible. (n=68). A total of	The AliveCor Heart Monitor and ECG App. The person’s phone, tablet, or watch was checked for compatibility, and they were asked to bring their smartphone, tablet, or watch and app store password to the ambulatory appointment (and later were asked to download the Kardia	Detection rate On the 1st assessment, a symptomatic cardiac dysrhythmia was detected in 6 (8.8%) patients. Three patients had supraventricular tachycardia (SVT; 4%), 2 had atrial fibrillation (3%), and 1 had atrial flutter (2%).	Included watch (mixed intervention)

	50 people who completed in the analysis. Follow-up: 90 days	app prior to coming to the clinic but not to set it up, which was done in the clinic.		
Dimarco *et al.* 2018 UK	Patients referred to our institution for investigation of intermittent palpitations but without syncope (n=148) Follow-up: March 2015 to June 2016	A Kardia Mobile device (with an access to a compatible smartphone. People were asked to record an ECG when symptomatic.	Detection rate • 113 (76.4%) people made symptomatic recordings during this period. A symptom-rhythm correlation was possible for all patients who submitted downloads. • Diagnoses were: sinus rhythm n=47 (41.6%), sinus tachycardia n=21 (18.6%), supraventricular/ventricular ectopics n=31 (27.4%), atrial fibrillation n=8 (7.1%), and supraventricular tachycardia n=6 (5.3%). The median time to diagnosis in those submitting symptomatic downloads was nine days (1–287 days). In the eight patients diagnosed with AF the median time to diagnosis was 12 days (1–66 days).	
Single-arm study (a mixed population)				
Bray *et al.* 2021 UK	People were eligible for inclusion if they had been referred to the Acute community Team with either known fast AF requiring monitoring and management, or with suspected AF due to an abnormal pulse on manual pulse check. (n=74, n=37 monitoring, n=53 diagnosis) Follow-up: 6 months	AliveCor—KardiaMobile	Detection rate • The 37 people requiring ECG monitoring for follow-up of fast AF had a total of 113 iECGs (median 1.5 ±3.75 per person). The majority of people only required one follow-up iECG to confirm adequate rate or rhythm control. There were no cases in which a 12-lead ECG was required due to the single-lead ECG not being sufficient. • Of the 53 patients assessed, 8 were found to have new onset AF, 19 patients with known AF (noted to be in sinus rhythm prior to index assessment) were found to have reverted back to AF, 7 had 'other' ECG abnormalities and 19 were normal.	Mixed population (management of known AF, and diagnosis of new AF). Acute Community Team members took measurements, which may not be generalisable to the general public.
Case -control study (people with AF) (n=1)				
Hickey et al. 2017, US	Case: people aged 21 years or older, with a documented history of AF and were scheduled to undergo a cardioversion, ablation, and/or medical management aimed at maintaining a normal sinus rhythm. (n=23) Control: people aged 23 years (within 5 years) and gender matched people with a documented history of AF	AliveCor ECG device. AliveECG application was downloaded to the patient's smartphone. People were asked to use the wireless ECG device at least daily (and when symptomatic) to record ECG readings, transmission time took less than 5 minutes per day.	AF/AFL detection rates • 14 patients in the ECG monitoring group (61%) and 7 patients in the control group (30%) had episodes of AF/AFL detected. Cox proportional hazard model analysis yielded a hazard ratio of 2.55 with a 95% confidence interval of 1.06 to 6.11, p = 0.04. Quality of life • Among the 13 people in ECG monitoring group who had QoL assessments at baseline and 6 months, PCS scores increased significantly from 50.3 +/- 7.6 to 55.9 +/- 5.3 (p = 0.02) while	Composite outcome (AF and atrial flutter)

	receiving usual cardiac medical care (no daily ECG self-monitoring) as part of their usual clinical management. (n=23) Follow-up: 6 months		MCS scores did not change significantly from baseline to 6 months (47.5 +/- 7.2 and 51.7 +/- 9.6, respectively). • Significant increases were observed for physical functioning, role physical, vitality, and mental health domain scores. Easy to use • None of the patients in the ECG monitoring group reported trouble using the device. In addition, 92% of respondents thought the device was beneficial and 58% said that they were more health conscious after participating in the study. Hospital resource use • There was no difference in the rate of hospitalizations between the ECG monitoring group and the control group. (no data reported in the study) Mortality No deaths occurred during follow-up.	
Case report (a person with AF) (n=1)				
Hickey et al/ (2013) US. The company provided the AliveCor Heart Monitor.	A 58-year-old Caucasian male with a prior history of atrial fibrillation (AF), hypertension, obstructive sleep apnea, congestive heart failure (CHF), peripheral vascular disease, and moderate alcohol consumption was admitted to a local Emergency Room (ER).	The AliveCor Heart Monitor	Detection of recurrent AF • The device had possibly detected recurrent AF. AF was detected at a rate of 118 bpm and the patient was given 20 mg of Cardizem intravenous ICardiac monitoring in the ER confirmed the results of the AliveCor device. The use of medicine • Upon discharge, the patient was given a new prescription for a higher dose of Metoprolol as well as an additional prescription for a calcium channel blocker to maintain his ventricular rate control.	Healthcare provider review of KardiaMobile trace instructed patient to attend nearest emergency room

4.2 Summary of economic evidence

The EAC included 3 published studies that are relevant to the decision problem (Praus et al. 2021; Reed et al. 2019; YHEC et al. 2018). Reed et al (2019) and YHEC (2018) were from an NHS perspective. The 3 published economic studies show that KardiaMobile would be cost saving due to a reduction in healthcare appointments during monitoring and diagnosis (emergency care, GP, ECG referral). Details and results of the 3 studies were described in Table 3, including an overview of comments from the EAC.

Table 3: Details and results of the 3 included studies with economic analysis.

Study, design, economic analysis	Population	Intervention & comparator	Results	EAC comments
Reed *et al.* 2019, open label, randomised controlled trial. UK-based; 10 emergency departments. Between 4 July 2016 and 9 January 2018. Not an economic model, is a cost calculator	People aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythm during these episodes remains undiagnosed after emergency department assessment. Follow-up: 90 days	Intervention: standard care plus the use of a smartphone-based event recorder. (n=124 available for analysis). Control: standard care (participants received no other intervention) (n=116).	Median overall healthcare utilisation cost primary/community/ secondary care and intervention costs) in the intervention group (KardiaMobile in addition to standard care) was £108 (IQR 99.0 to 246.50, range 99 to 2697) versus £0 in the standard care group (IQR 0 to120.0, range 0 to 4161; p = 0.0001). Cost per symptomatic rhythm diagnosis was £921 less per person per symptomatic rhythm in the intervention group (£474) compared to the control group (£1395).	There was potential for bias in healthcare costs. This is due to local study team advising GP follow-up in cases where specialist follow-up of the ECG was not required, and thus increasing costs in the intervention arm only. The cost per symptomatic rhythm diagnosed was £921 less per person in the intervention group (£474; n=69) compared with the control group (£1,395; n=11). However, this study, and the costs calculated, included all symptomatic rhythms (sinus rhythm, sinus tachycardia, ectopic beats, AF, supraventricular tachycardia, atrial flutter, sinus bradycardia, atrial tachycardia, ventricular tachycardia, and other rhythms). Therefore the EAC considered that KardiaMobile may provide additional healthcare benefits in supporting the detection or rule-out of other cardiac arrhythmias (**however this is out of scope of this assessment**).
Praus *et al.* 2021 US-based Costing analysis added to a single-arm observational study recruiting from clinic.	Adult who had two or more AF-related ED or UC visits in the past 12 months, needed rate control with medication titration, or needed monitoring for AF reoccurrence after reestablishing sinus rhythm—either by chemical or direct current cardioversion. (n=43) Follow-up: 8 weeks	A KardiaMobile (KM) device. People instructed to send daily readings and whenever symptomatic.	The study projected a savings of $81,950 from a reduction in emergency visits. The estimate was based on the results of the patient questionnaire reporting 34% (n = 11) people who would visit emergency visits if KardiaMobile was not available	Mixed intervention. Not generalisable to NHS.
YHEC 2018 “NHS Innovation Accelerator: Economic Impact Evaluation Case	People with a suspected arrhythmia, such as atrial fibrillation (AF) in a primary care setting.	Intervention: KardiaMobile pathway; The cost of Kardia pathway is assumed to include the full cost of the KardiaMobile device (which intrinsically assumes each person	The analysis suggested that the KardiaMobile pathway (£171) saved £968 per person investigated when compared with the typical pathway (£1,139) due to fewer appointments and investigations.	The EAC consider this cost saving (of £968) as unlikely, as some people on the typical pathway may receive a clinical diagnosis during the pathway and thus not require the full number of appointments and investigations included in this evaluation. The evaluation reported lower savings of £399 per person when only

Study: AliveCor Kardia Mobile" UK-based Not a peer-reviewed publication	1 year time horizon	has a new device) and 2 GP appointments only. Comparator: typical AF pathway in the NHS. The cost of a typical AF diagnostic pathway in the NHS was calculated to estimate: - the impact of avoided healthcare appointments assuming the following visits needed: • 2 GP appointments • 1 cardiology outpatient appointment • 2 cardiology follow-up appointments -the impact of avoided cardiology investigations assuming the following investigations need: • a 12-lead ECG • a 24-hour ECG and • 7-day ECG	Sensitivity analysis: if device was reused by multiple patients, there was a larger cost saving.	50% of people needed all of the tests in the typical AF pathway. Following the recommended clinical pathway for palpitations, KardiaMobile should be used after inconclusive 12-lead ECG, and may be used after Holter monitoring (increasing costs in the KardiaMobile arm). If KardiaMobile was adopted for 250 people per year, the economic evaluation calculated total savings of £242,000 per year. Sensitivity analysis was also carried out, and found that £96,800 could be saved per year if only 100 people followed the KardiaMobile pathway. The base case assumed that each KardiaMobile device was used by only one person, but if the same device was used in a GP consulting room for 100 people per year, this saving would rise to £106,601 per year. The EAC notes that this evaluation only considers costs of appointments avoided during the diagnosis phase and does not consider cost of AF management and reduction in strokes, which would likely increase the cost saving associated with KardiaMobile.

De novo analysis

The company developed a de novo model that compared the costs and health outcomes associated with monitoring for AF using KardiaMobile with other alternative technologies including Holter monitoring (24 hours, 48 hours and 7 days) and Zio patch electrode monitor (14 days) in adults aged 64 years or above with known, or suspected AF who were referred for ambulatory ECG monitoring in a secondary care setting.

The model consisted of 2 Markov models representing:

- an AF diagnosis phase using time dependent transitions (maximum 100-day time horizon using a 1-day cycle length).
- subsequent management phase (5-year time horizon using a 1-year cycle length).

The company's model assumed that only people receiving a positive result by KardiaMobile would have a follow-up visit with a GP or cardiologist. While all monitoring tests with Holter, Zio or continuous event recorder (CER) would be followed-up with an outpatient clinic visit (GP or specialist), regardless of findings. People with negative and confirmed positive results by the clinician would not repeat ambulatory ECG. Where repeat ECG monitoring would be needed in people with undiagnosed AF, the same device (always in the case of KardiaMobile) or an alternative technology may be used (e.g., CER after Holter 24h) following the initial monitoring. The use of an implantable device could be an option when there is a significant concern. The model assumed a maximum of 2 repeat tests, including implementable loop recorders (LRs) after the initial test.

The main parameters included in the company's model were:

- AF prevalence, 30%
- Duration of monitoring with KardiaMobile and the comparator (Zio patch), 14 days, and 30 days for CER

- Waiting time for diagnosis with KardiaMobile and the comparators (Holter, Zio patch, CER), 3 days
- Rate of repeat monitoring after Holter, Zio patch and CER, 0.27, 0.176 and 0.179.

The cost of KardiaMobile in the company's submission is calculated as £124.00 (including cost of KardiaMobile hardware, app free of charge). The device cost per monitoring was estimated at £9.53, which was based on the device being used up to 38 times over its 2 year life span plus 10 minutes nurse time for preparing the device and to deliver patient training (band 6 nurse at £47 per hour). The company included the costs associated with health service visits (GP, nurse and cardiologist) and ECG monitoring by Holter, Zio service, CER and loop recorder in the diagnostic phase of the model. In the management phase of the economic model, the costs of using medication (aspirin, warfarin and NOACs) if diagnosed with AF and treating clinical adverse events including stroke, myocardial infarction, intracranial haemorrhage, major bleeding were included.

Company base case results

The company base-case showed that KardiaMobile ECG monitoring was cost-saving over 5 years compared with Holter and Zio Service patch (see Table 4).

Table 4: company base case results.

	Total cost	Cost difference
KardiaMobile + Clinician	£2,941.19	
Holter (24-hour)	£3,262.69	-£321.50
Holter (48-hour)	£3,260.94	-£319.75
Holter (7 days)	£3,273.84	-£332.65
Zio patch (14 day)	£3,323.99	-£382.80

The company also conducted deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) for the base case and report that all sensitivity analyses resulted in KardiaMobile being cost saving. In the company's one-way sensitivity analysis, comparing KardiaMobile with 24-hour Holter monitoring (including repeat monitoring with different devices), the variables with the largest impact on incremental cost were:

- probability of AF positive (KardiaMobile + Clinician),
- proportion of patients on NOAC, and
- probability of diagnostic yield (24-hour Holter)

The PSA also demonstrated that KardiaMobile was cost-saving compared with clinical interpretation of the ECG, Holter monitoring (24-hour, 48-hour and 7-day) and Zio patch.

The company reported quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs). KardiaMobile resulted in increased survival, and increased QALYs gained compared with Holter and Zio patch over a five-year time horizon.

EAC critique of the company model

The EAC critically appraised the company model. KardiaMobile was presented as cost-saving when compared to Zio and Holter monitoring. Clinical experts advised that 24 hours was most common for Holter monitoring. The EAC was not able to replicate the model presented by the company which limited the assessment of the de novo analysis and certainty in the results presented. The Markov states provided by the company in its illustration of the model structure did not fully reflect the Markov states which were used in their calculations. Some parameter values and assumptions were not explicitly described in the company's economic submission. The company confirmed that more than a dozen values described in the submission were not applied or were incorrect and differed from the actual values applied in the model. The EAC considered the model structure to be

overcomplicated and felt that there was no robust evidence to support the complex time dependencies in the diagnostic phase of the model.

The EAC considered a 5-year time horizon for the management phase to capture long-term outcomes to be appropriate in some sub-groups given the impact of diagnosing AF on reducing subsequent strokes. This was confirmed by clinical experts. There was no published long-term evidence included in the company submission which demonstrated reduction in strokes or mortality directly associated with the KardiaMobile device. The company did not provide justification for a maximum 100-day time horizon for the diagnosis phase in the model.

The EAC disagreed with the assumption that all monitoring tests with Holter, Zio or CER would be followed-up with an outpatient clinic visit regardless of findings. The EAC considered that an outpatient appointment would normally only be needed after a significant positive result, regardless of the ECG monitoring device used. Other assumptions in the model and corresponding EAC comments are in section 9.2.2 (page 87) of the assessment report. The EAC considered some of these assumptions could lead to bias in favour of KardiaMobile in the economic analysis and additional assumptions made within calculations of the model were not explicitly described in the company submission.

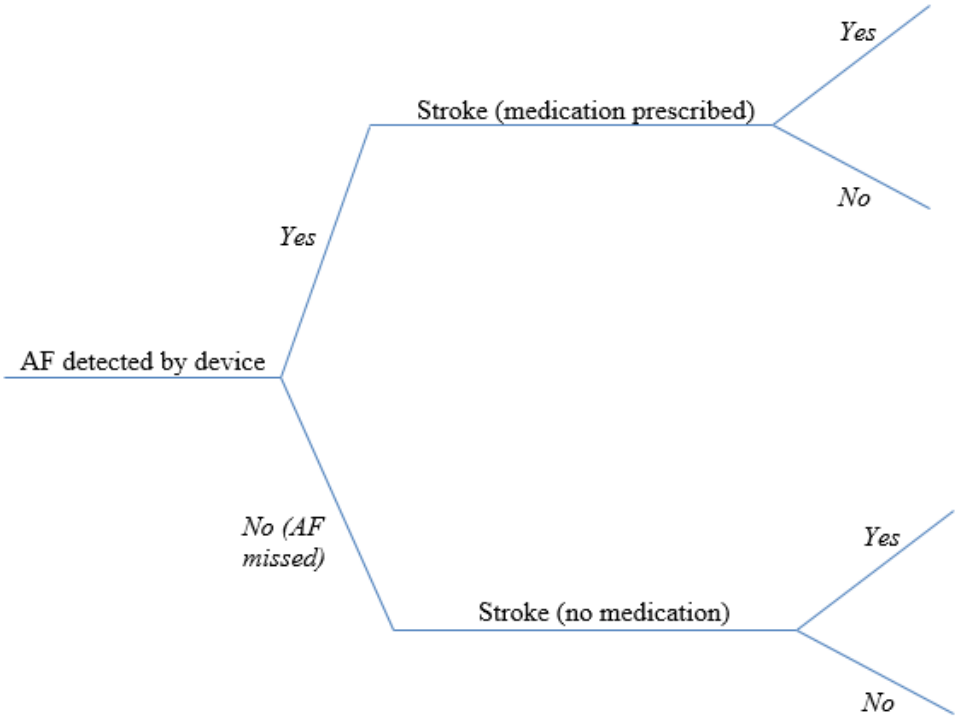
The EAC considered some parameters used in the model were unlikely to reflect the variation in current NHS practice. The model included a 14-day monitoring period using KardiaMobile with a 3-day wait time for a diagnosis. The clinical experts noted the time intervals between a person emailing an ECG and it being reviewed varied in clinical practice from 1 working day to once a week or at the end of monitoring. A maximum of 2 repeated sessions of monitoring were permitted in the model. The consensus from the clinical experts was that 2 repeated monitoring tests was unlikely, with one expert stating that they use only a single diagnostic test per patient. One expert stated that repeat testing was applicable across all patient subgroups.

The 30% AF prevalence for a diagnosis model over 100 days was not supported by the evidence. AF prevalence reported in the published studies varied from 6.5% in people presented with undiagnosed palpitations to 60.9% in those with AF recurrence after treatment. The EAC also identified a number of discrepancies between the values described in Table 4 company economic submission and the values implemented in the model, which the company confirmed were a consequence of complexity and updated iterations of the model. The experts considered the values of gastrointestinal bleed rates for AF people who were on medications including aspirin, warfarin and novel oral anticoagulants (NOAC) used in the model were incorrect.

EAC cost calculator

The EAC disagreed with the structure and some of the underlying assumptions of the company's economic model. Because the EAC was unable to replicate the model and it could not be amended to address some of the limitations identified. The EAC created a simple cost calculator to explore the potential cost consequence of using KardiaMobile to detect AF over a 1 year time horizon compared with standard care, Holter monitoring and external loop monitoring. The general approach to the cost calculator is illustrated by a simple decision tree (se figure 3).

Figure 3: Structure of the EAC cost-calculator.



The calculator assumes that

- KardiaMobile ECG recording interpreted by a clinician has 100% sensitivity and 100% specificity
- ECG review time was considered broadly equal in both arms (excluded from the analysis)
- 6 diagnostic yield scenarios based on 6 comparative studies (included in the clinical submission)
- Increased AF detection from 3 RCTs and 1 case-control study are an estimate as the data are not paired
- Risk of stroke is determined from CHA_2DS_2-VASc score

The main parameters used in the EAC calculator were the device costs, AF detection rate, risk of stroke in untreated AF, and risk reduction to stroke in treated AF.

In the EAC calculator, the cost of KardiaMobile (single lead version) device is £82.50 with 8 times use over a 2-years expected device life (maximum of 90

days monitoring per patient (730/90). The EAC included a training cost of £12.50 for 15 minutes nurse time (band 6 nurse at £50 per hour) and a Holter monitoring cost of £176.42 (NICE MTG 52, 2020). The cost of anticoagulation (including bleeding) and treating cost were also included in the calculator (details see Table 23 on page 111 of the assessment report).

The EAC applied 6 scenarios based on 6 comparative studies with various population size and AF detection rate, and KardiaMobile was found to be cost saving compared with Holter or external loop recording in 3 scenarios; with a saving ranged from £144 to £490 per person (see Table 5 below).

The scenario based on Reed et al. (2019), an open label RCT, resulted in an additional £32 per person using KardiaMobile in addition to standard care compared with standard care alone. The EAC considers that this scenario represents the cost of the KardiaMobile when used as an additional diagnostic (that is as an additional test used alongside Holter monitoring). The remaining scenarios (Goldenthal et al. 2019 and Hickey et al. 2017) measured AF recurrence following treatment, and standard care was not defined, thus zero device costs were included for the comparator arm. Therefore, if the per-person cost in the comparator arm exceeds £41 and £71, respectively, KardiaMobile is likely to to be cost saving.

Table 5: Cost consequence analysis in 6 scenarios based on 6 comparative studies

Scenario	Population	Comparator	AF detection (intervention)	AF detection (comparator)	Difference in AF detection	Intervention cost (per person)	Comparator cost (per person)	Differences in cost per person[1]
Hermans *et al.* 2021 Netherlands (n=115)	AF recurrence	3 rounds of min. 24-hour Holter	25.2%	14.8%	10.4%	£140.69	£630.76	-£490.08
Narasimha *et al.* 2018 US (n=33)	Palpitations	External loop recorder	18.2%	12.1%	6.1%	£107.80	£251.90	-£144.10
Koh *et al.* 2021 Malaysia (n=203)	Stroke/TIA	Additional round 24-hour Holter	9.5%	2.0%	7.5%	£67.33	£211.31	-£143.98
Reed *et al.* 2019 UK (n=240)	Palpitations	Standard care	6.5%	0%	6.5%	£52.97	£21.42	£31.55
Goldenthal *et al.* 2019 US (n=233)	AF recurrence	Standard care (undefined)	50.4%	41.5%	8.9%	£258.56	£217.79 (unknown device costs)	£40.77
Hickey *et al.* 2017 US (n=46)	AF recurrence	Standard care (no ECG monitoring; undefined)	60.9%	30.4%	30.4%	£307.33	£236.78 (unknown device costs)	£70.55
Abbreviations: AF atrial fibrillation; ECG electrocardiogram; TIA transient ischaemic attack; 1. A negative value indicates a saving.								

The EAC ran a sensitivity analysis to explore the impact of the risk of stroke (measured by CHA_2DS_2-VASc score) and the KardiaMobile monitoring period on the 6 scenarios. Cost savings increased with CHA_2DS_2-VASc score (Hermans et al. 2021; Koh et al. 2021, Narasimha et al. 2018). All scenarios became cost saving when a score of 6 was applied (risk of stroke 9.8%). The direction of cost saving and cost incurring remains unchanged even when varying the KardiaMobile use from 7 days to 90 days per person (see Table 26 and 27 on page 115 to 116 of the assessment report).

Summary

The evidence from the published economic studies showed that the use of KardiaMobile was associated with an expected cost saving, due to a reduction in clinical appointments during detection (emergency care, GP, ECG referral). The company base-case results suggested that using KardiaMobile would save £322, £320, £333 and £383 per person over 5 years when compared with 24 hour, 48 hour, 7 day and 14 day Zio patch monitoring respectively. The EAC was not able to replicate the company model and address the limitations identified, therefore the results are uncertain. The EAC carried out an exploratory analysis using a cost-calculator to assess the comparative costs of KardiaMobile over a 1 year time horizon populated by the 6 comparative clinical studies. The results of the cost calculator found KardiaMobile to be cost-saving between £144 and £490 per person when compared with Holter or external loop recorders in 3 scenarios driven by increased detection of AF with KardiaMobile and the predicted number of strokes avoided at 1 year.

5 Patient survey

NICE's public involvement programme circulated a survey to explore people's experience using KardiaMobile between 14 April to 28 May 2021. A total of 141 responses were received. Results from responders were extracted and are summarised Appendix C.

6 Ongoing research

The company identified 15 ongoing studies. The EAC excluded 7 of these (details see appendix D1 of the assessment report).

In addition to 8 studies identified by the company, the EAC found additional 5 studies. Therefore, there are a total of 13 on-going studies on the device (see appendix D2 of the assessment report). The EAC noted that none of the ongoing studies are based in the UK. The 3 largest ongoing studies including, an observational study including 3000 patients(NCT04404465), and 2 RCTs (NCT03713333, NCT03323099) are all set in the US, and have included KardiaMobile within a digital healthcare bundle making it difficult to measure the direct impact of KardiaMobile.

7 Issues for consideration by the Committee

Clinical evidence

- A total of 32 publications were relevant to the decision problem. But these studies were heterogeneous in nature, had different population groups across different settings. The use of KardiaMobile varied in the studies with different frequencies and durations.
- Definition of standard care varied across studies.
- The diagnostic accuracy was not analysed at a patient level, and the analysis was based on the number of ECG recordings.
- Three RCTs including 2 trials reported AF detection rate, showing that the rate was significantly higher in people used KardiaMobile compared with those had standard care. One trial reported the rate in combined AF and AFL.

- Two RCTs report that KardiaMobile reduced time to AF detection when compared to standard care. However, time to AF detection is influenced by how frequently people advised to use the device, and how quickly ECGs traces are subsequently reviewed by a healthcare professional.
- Limited evidence to suggest KardiaMobile leads to improvements in quality of life (2 RCTs included multiple interventions).
- None of the included studies reported on the use of KardiaMobile-6L.

Cost evidence

- The published 3 studies including 2 UK studies reported the use of KardiaMobile to be cost saving, largely through the reduction in healthcare appointments (emergency care, GP, ECG referral). No published evidence reported the impact of using KardiaMobile on long term clinical outcomes such as the reduction in stroke.
- There is no published evidence directly comparing the diagnostic performance of KardiaMobile with the Zio patch.
- The company base case model showed KardiaMobile to be cost saving in adults who are symptomatic, referred for ambulatory ECG monitoring in secondary care compared with Holter or Zio patch. But the EAC considered the model results as untransparent and unverifiable. It was not able to independently replicate the model.
- The EAC's cost-calculator showed KardiaMobile to be cost-saving in 3 scenarios, ranging between £144 and £490 per patient when compared with Holter or external loop recorder monitoring due to the increased rate of detection of AF with KardiaMobile, resulting in avoidance of strokes. But the absence of a verifiable model means that there are uncertainties over the magnitude and confidence interval of savings for different scenarios.
- The cost calculator did not consider risk reduction due to novel oral anticoagulants (NOACs).
- Two scenarios informed by Goldenthal et al. 2019, Hickey et al. 2017) did not include a comparator device cost because of a lack of adequate information.

8 Authors

YingYing Wang, Dionne Bowie, Health technology assessment analysts

Lizzy Latimer, Kim Carter, Health technology assessment adviser

NICE Medical Technologies Evaluation Programme

June 2021

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

A Details of assessment report:

Kim Keltie, Michael Drinnan, Alex Inskip, Fiona Beyer, Rachel O'Leary, Grace Fairlamb, Julie Burn, Derek Bousfield and Andrew Sims. Newcastle External Assessment Centre

B Submissions from the following sponsors:

AliveCor Ltd

C Related NICE guidance

- Atrial fibrillation: diagnosis and management. NICE guideline (NG196 (2021). Available from https://www.nice.org.uk/guidance/ng196.
- Transient loss of consciousness ('blackouts') in over 16s. NICE clinical guideline (CG109) (2014). Available from https://www.nice.org.uk/guidance/cg109/.
- Zio XT for detecting cardiac arrhythmias. NICE medical technology guidance (MTG 52) (2020). Available from https://www.nice.org.uk/guidance/MTG52.
- Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care NICE diagnostics guidance (DG35) (2019). Available from https://www.nice.org.uk/guidance/dg35.

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York Health Economics Consortium. NHS Innovation Accelerator. Economic Impact Evaluation Case Study: AliveCor Kardia Mobile

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

- Adrian Brodison, clinical lead cardiology, University hospitals of Morecambe bay NHS Foundation Trust.
- David Ferguson, arrhythmia advanced nurse practitioner, University Hospitals of Morecambe Bay NHS Foundation Trust.
- Kevin McGibbon, arrhythmia clinical nurse specialist, North Midlands NHS Trust.
- Lis Neubeck, professor of cardiovascular health, School of Health and Social Care, Edinburgh Napier University.
- Matt Reed, consultant in emergency medicine, NHS research Scotland clinician and RCEM Professor of Emergency Medicine, NHS Lothian.
- Dr Ruth Chambers, clinical lead for technology enabled care lead for Staffordshire Sustainability and Transformation Partnership.
- Shona Holding, cardiovascular advanced nurse practitioner, Affinity care.
- Dr Shouvik Haldar, consultant cardiologist & electrophysiologist, Royal Brompton & Harefield Hospitals.

Please see the clinical expert statements included in the pack for full details.

Appendix C: Results from the patient survey

During April–May 2021, NICE's public involvement programme posted an online survey, 141 responses were received. All responders confirmed that they read the information sheet provided which explains the purpose of the survey and how the information will be used. All responders consented to NICE using the information as described.

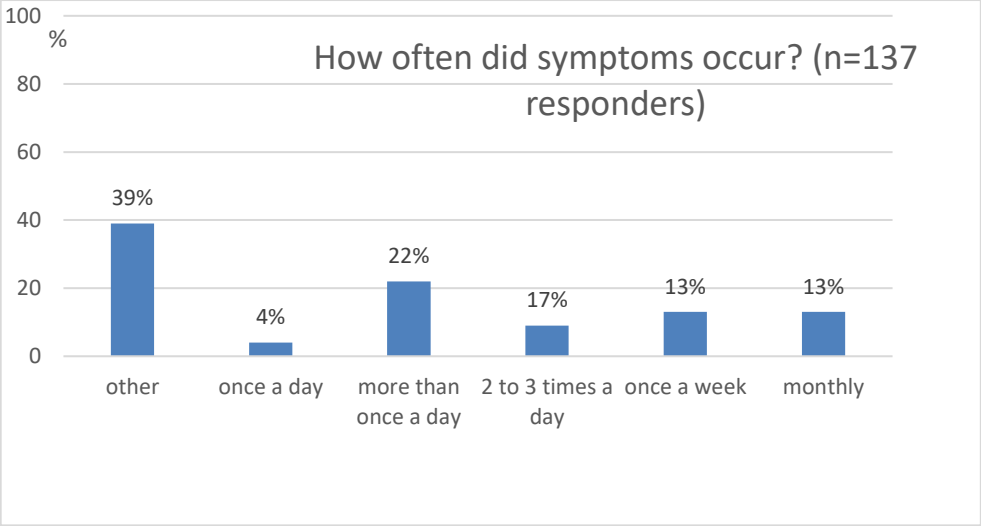
1. Responder demographics

Mean age of responders was 67.8 years, range 34–80 years. 36.9% of responders were male (n=52) and 62.4% were female (n=88).

2. Symptoms

Most responders experienced rapid and/or irregular heartbeats (n=132). Other common symptoms were dizziness, light headedness, shortness of breath while exercising or walking.

Only a small proportion of responders had their symptoms once a day (n=6, 4%), and 22% experienced symptoms more than once a day (n=30, 22%).



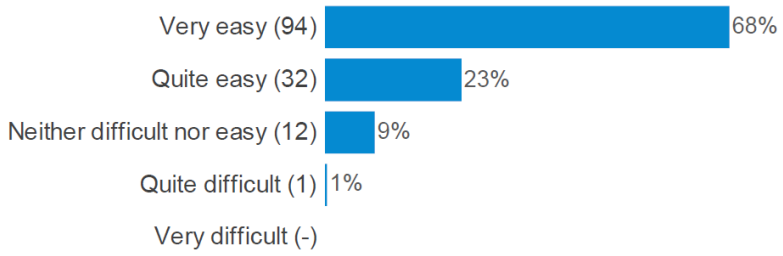
3. KardiaMobile ECG monitoring

Responders had been prescribed the KardiaMobile device to help detect irregular heartbeats by their GPs (23.3%, n=31) or by a hospital cardiac consultant (31.6%, n=42). Some purchased the KardiaMobile device themselves (22.6%, n=32). Over 60% responders (n=62, 66%) used KardiaMobile for the full amount of time they were loaned the device. Most responders used it when they had symptoms or when they felt need to self monitor their heart rates (n=103, 73.0%).

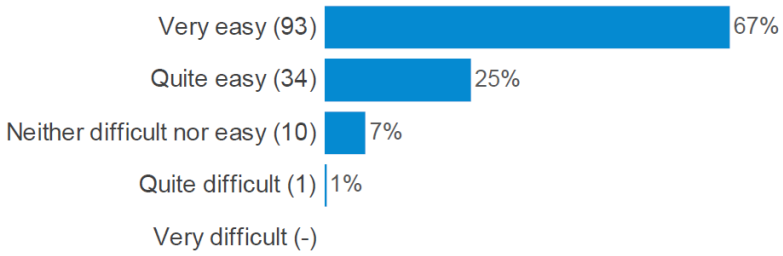
4. Experience of using the device

The majority of responders (n=126, 89.4%) found easy to use KardiaMobile and easy to follow its instruction for use (n=127, 90.0%). Most responders thought straightforward transfer ECG trace to health care professionals (n=84, 58.6%) but 8 people found the transferring quite difficult (6.1%).

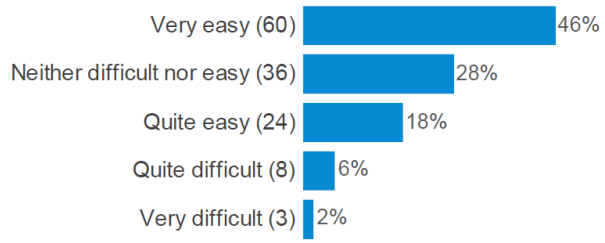
How easy was using the KardiaMobile device and app?



How easy to follow were the instructions for use?



How straightforward was transferring ECG trace to health care professionals?



Most responders did not experience any side effects after using the device however 4 responders (2.8%) reported side effects for example one thought the conclusion was not informative and the other thought sometime difficult to get clear trace.

Many responders also used other ECG monitors (n=61, 43.3%) including Holter monitor, external event monitor and implantable event monitor. Of them, they felt that KardiaMobile was compact, more convenient and provided instance feedback compared with other monitors.

Responders also described the positive effects and negative effects of using the KardiaMobile device. Some quotes from the responders as following:

Main positive effects

"*I can readily measure my ECG and share with my Consultant Also I was admitted to A & E twice based on the evidence of the Kardia and on both occasions required and electrocardioversion*."

"Being able to quickly confirm that I am in AFib. Being able to quickly send information to the Cardiac team. Being confident that I have the readings to hand when needed and not having to wait for a monitor or an ecg appointment."

"*It allows me to monitor my heart rate in AF so I can judge when to take extra medication, go to A&E etc*."

"*I can tell from my Kardia when to seek medical intervention for AF - although I usually sit it out Other than presenting to A&E I have no other medical supervision of AF so it is a useful reassurance*."

"*Can't always catch AF instantaneously as you can with watch app and it's not always convenient to take a reading with Kardia when out and about. Also must not rely completely on it because a hospital ECG will always be more accurate*"

Main negative effects

"*Temptation at first to use it too much to keep checking*"

"*Need input on how to read the device correctly*"

"*Can't always catch AF instantaneously as you can with watch app and it's not always convenient to take a reading with Kardia when out and about. Also must not rely completely on it because a hospital ECG will always be more accurate*"

"*I have found it needs heavy and very still finger presssure in order to get a good clear trace and this can be difficult for somebody of my age*"

"*I've had my Kardia since they came available on the market. The only negative- Kardia does not work well on quartzite counters. Says electrical interference. Never had this problem before I replaced my kitchen countertops*"

"*a lot of readings had interference or unclassified which had to retake multiple times*"

Appendix D: decision problem from scope

	Final scope issued by NICE
Population	Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care.
Intervention	The KardiaMobile system: KardiaMobile hardware (single-lead or 6 lead ECG monitor) and KardiaMobile app. Single time point detection of atrial fibrillation is not included in the scope of this evaluation. The analysis should explore the impact of using the technology algorithm for trace classification, or interpretation of the ECG trace for detecting atrial fibrillation.
Comparator(s)	Current pathway for atrial fibrillation detection, which includes ECG (a 12-lead ECG, performed and interpreted by a trained healthcare professional, is the reference standard for assessing diagnostic accuracy) and ambulatory monitoring (Holter and/or event monitoring).
Outcomes	The outcome measures to consider include: System outcomes Diagnostic yield and accuracy (sensitivity and specificity) Atrial fibrillation burden, including the number of symptomatic and asymptomatic atrial fibrillation events detected during the recording period, and the time spent in atrial fibrillation Time to detect first or recurrent atrial fibrillation events Time to diagnosis or rule out of atrial fibrillation Time to initiation of treatment (control symptoms and/or preventing the risk of future events) Rate of test failure Data transfer failure Rate of fail to classify Rate of secondary care referral Total number of hospital outpatient appointments for investigation Hospital admission Number of outpatient visits and staff time for undertaking and analysing diagnostic tests Number of visits to GP or urgent care Number of further tests needs in addition to KardiaMobile Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment) Mortality Patient outcomes: Ease of use (for patients and healthcare professionals), including training requirements Device acceptability and patient satisfaction Health-related quality of life Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective.

	The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	Adults referred for ambulatory ECG monitoring, who are symptomatic or asymptomatic Adults referred for ambulatory ECG monitoring in primary care Adults referred for ambulatory ECG monitoring in secondary care	
Special considerations, including those related to equality	KardiaMobile is not approved for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices. The device may not be suitable for people who cannot remain still or have problems holding the device; for example, people with tremor may have difficulty with recording an accurate trace. People are not able to use the device if they do not have a compatible smart device to access the KardiaMobile app. Age and disability are protected characteristics under the Equality Act. Full details of contraindications are listed the instructions for use for KardiaMobile.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	Cardiac arrhythmias can develop in people of any age but are more common in people over 60 years. The lifetime risk of developing atrial fibrillation is similar for both men and women, although it is slightly higher in men. Age and sex are protected characteristics under the Equality Act. People whose first language is not included in the app or who cannot read may not be able to communicate recorded information on their symptoms while using the KardiaMobile system. The app is available in the following languages including English, German, Dutch, Spanish, French, Italian, Norwegian (Bokmål), Chinese (simplified or traditional), and Korean.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

KardiaMobile for detecting atrial fibrillation

1 Technology

1.1 Description of the technology

KardiaMobile (AliveCor) is a portable electrocardiogram (ECG) recorder. It works with a compatible mobile device (such as a smartphone or tablet,) running the Kardia app, which is intended to be used for analysing the ECG recording and sending it to a healthcare professional for interpretation.

KardiaMobile is available as a single-lead or as a 6-lead (KardiaMobile 6L) ECG recorder. The single-lead version has 2 electrodes on the top surface; 2 fingers from the left hand are placed onto 1 electrode and 2 fingers from the right hand are placed onto the other electrode. KardiaMobile 6L has 3 electrodes; 2 electrodes on the top surface (for 2 fingers from each hand), and one on the bottom which is placed on the left leg. The device is small and is designed to be used anywhere that is convenient.

People must keep their arms still and must keep touching the electrodes for at least 30 seconds for a complete reading to be taken. The app has an option for either single-lead or 6-lead ECG reading. The company recommends that recordings are taken daily at random, or whenever symptoms are experienced that may be atrial fibrillation (AF). There is no restriction on the number of times the device should be used. Healthcare professionals may advise people on the frequency and length of use.

Internet access is not needed when taking the reading. While taking a reading, the ECG recoding is sent wirelessly to the mobile device, where it can be viewed using the Kardia app. The app works on devices running Apple or Android operating systems (a full list is available on the compatibility

section of the company's website). It shows the ECG trace, a measure of heart rate, and it uses an artificial intelligence led algorithm to classify the traces as:

- normal
- possible AF
- tachycardia
- bradycardia
- sinus rhythm with premature ventricular contractions (PVCs)
- sinus rhythm with supraventricular ectopy (SVE)
- sinus rhythm with wide QRS or
- unclassified.

ECG traces measured by the device can be sent from a smartphone or tablet by email as a PDF attachment and stored in a patient's records to be shared with healthcare professionals. Patient data can be added to the recording in accordance with information governance and the general data protection regulations (GDPR). When the device has a Wi-Fi or mobile connection, the recording automatically synchronises with a secure encrypted cloud server (this can be turned off manually from the device). An option (additional fee) for healthcare professionals is the KardiaPro software, which allows remote monitoring of users and generation of reports.

KardiaMobile is not intended for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices. The company states that the ECG recorded by KardiaMobile is used to help diagnose heart rhythm disturbances but is not intended to be used to diagnose other cardiac conditions. The interpretations should be reviewed by a medical professional and used to support clinical decision-making.

The average lifespan of the single-lead and 6-lead devices is 2 years. The technology has previously been known as AliveCor Heart Monitor and AliveCor Mobile ECG. A smartwatch band, KardiaBand, has been discontinued and is not included in the scope of this evaluation.

1.2 Relevant diseases and conditions

KardiaMobile is designed for use in adults to detect abnormal heart rhythms (cardiac arrythmia) via single time point testing or longer term monitoring to support clinical decision-making. This guidance focuses on the use of KardiaMobile for detecting atrial fibrillation by ECG monitoring. NICE diagnostics guidance (DG35, 2019) assessed on the use of lead-I ECG devices (including KardiaMobile) for detecting symptomatic atrial fibrillation using single time point testing in primary care. Therefore, single time point detection of atrial fibrillation is not included in the scope of this evaluation.

Cardiac arrythmias are experienced by more than 2 million people a year in the UK. The term covers a number of conditions in which the heartbeat is irregular, too fast or too slow. Common types of arrhythmia are atrial fibrillation, supraventricular tachycardia, bradycardia, heart block and ventricular fibrillation (NHS, 2018).

Atrial fibrillation is the most common sustained cardiac arrhythmia. It has been estimated that 1.4 million people in England have atrial fibrillation, equating to 2.5% of the population. The likelihood of atrial fibrillation increases with age. The prevalence of atrial fibrillation is higher in men than in women (2.9% compared with 2.0%). People with atrial fibrillation may present with breathlessness, heart palpitations and dizziness or temporary loss of consciousness. The frequency and severity of symptoms varies from person to person and symptoms of a person can also fluctuate widely over time. These changes can be monitored via ECG. Atrial fibrillation can also be asymptomatic. It is estimated that around 425,000 people in England have undiagnosed and untreated atrial fibrillation (Public Health England, 2017).

Atrial fibrillation is associated with an increased risk of thrombo-embolic complications including stroke as well as the need for hospitalisation, and death. Untreated atrial fibrillation is associated with a 5-fold increased risk of stroke and a 3-fold increased risk of heart failure (European Society of Cardiology, 2012).

1.3 Current management

In clinical practice, an electrocardiogram (ECG) is commonly used to diagnose an arrhythmia. An ECG is done in a general practice or hospital setting and records heart rhythm over a short period of time. If the ECG doesn't reveal an abnormality at that moment in time, the person's heart rhythm may need monitoring for a longer period of time. This may involve wearing a small portable ECG recording device for 24 hours or longer. This is often known as a Holter monitor or ambulatory ECG monitoring. Alternatively, cardiac event recorders may be used in patients with occasional symptoms. These are either a portable device to record the heart rhythm at the time of symptoms using a device that is worn strapped to a person's body and may require electrodes to be stuck to the skin, or a device that is implanted under the skin.

NICE's guidelines on managing atrial fibrillation and transient loss of consciousness ('blackouts') in over 16s provide recommendations on current methods of arrhythmia detection.

The NICE guideline on managing atrial fibrillation recommends performing manual pulse palpation to assess for the presence of an irregular pulse in people presenting with any of the following:

- breathlessness/dyspnoea
- palpitations
- syncope/dizziness
- chest discomfort
- stroke/transient ischaemic attack

It is recommended that an ECG be performed in all people, whether symptomatic or not, in whom atrial fibrillation is suspected because an irregular pulse has been detected. Arrhythmias may be missed by a 12-lead ECG in people with paroxysmal AF (that is, intermittent AF) because of the occasional nature of the arrhythmic episodes. If arrhythmia is not detected on the initial 12-lead ECG and further assessment of suspected paroxysmal atrial

fibrillation is needed then ambulatory ECG monitoring is recommended. The choice of monitor used depends on the nature and frequency of symptoms.

The guideline recommends the following:

- use a 24-hour ambulatory ECG monitor (such as a Holter monitor) in people with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
- use an event recorder ECG (which can be external or implantable) in people with symptomatic episodes more than 24 hours apart

For people with transient loss of consciousness (TLoC) and a suspected cardiac arrhythmia (including AF), the NICE guideline on transient loss of consciousness ('blackouts') recommends offering an ambulatory ECG. The type of device should be chosen on the basis of the patient's history and frequency of TLoC. Holter monitoring (up to 48 hours if necessary) is recommended in people who have TLoC at least several times a week. In those with TLoC every 1 to 2 weeks an external event recorder should be offered. An implantable event recorder should be offered to people with infrequent TLoC (less than once every 2 weeks).

The company states that KardiaMobile is intended to replace or enhance the current care pathway for detecting atrial fibrillation in patients with symptoms such as palpitations and TLoC but that the device can also be used to assess the adequacy of treatment for AF when this has been offered. KardiaMobile would be used for a monitoring period predetermined by a physician in place of current methods of cardiac event detection, such as Holter monitoring or event recording in people suspected of having atrial fibrillation. The use of KardiaMobile would be recommended by a clinician, most often a cardiologist or GP, in primary, secondary or tertiary care.

1.4 Regulatory status

The KardiaMobile single-lead heart monitor and Kardia app received a CE mark in January 2018 as a class IIa medical device for recording single-lead ECG for identifying ECG rhythms. KardiaMobile 6L heart monitor received a

CE mark in August 2019 as a class IIa medical device for recording six leads ECG for identifying ECG rhythms.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Improved identification of people with atrial fibrillation, potentially leading to a reduction in the occurrence of clinical sequelae of atrial fibrillation such as stroke and heart failure.
- Improved diagnostic accuracy and efficiency in detecting atrial fibrillation in symptomatic and asymptomatic patients.
- Improved diagnostic yield, minimising the number of repeat tests needed to confirm or rule out atrial fibrillation.
- Earlier diagnosis and potential initiation of treatment to control atrial fibrillation or prevent the occurrence of clinical sequelae of atrial fibrillation such as stroke and heart failure.
- Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

The benefits to the healthcare system claimed by the company are:

- Reduction in costs and resources that could be avoided through earlier diagnosis and treatment of atrial fibrillation, such as repeat hospital admissions related to the clinical sequelae of atrial fibrillation, such as stroke or heart failure.
- Avoiding unnecessary referral to secondary care.
- Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.
- Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduced in-clinic analysis of ECG recordings and reduced outpatient appointments.

2 Decision problem

Population	Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care.
Intervention	The KardiaMobile system: KardiaMobile hardware (single-lead or 6 lead ECG monitor) and KardiaMobile app. Single time point detection of atrial fibrillation is not included in the scope of this evaluation. The analysis should explore the impact of using the technology algorithm for trace classification, or interpretation of the ECG trace for detecting atrial fibrillation.
Comparator(s)	Current pathway for atrial fibrillation detection, which includes ECG (a 12-lead ECG, performed and interpreted by a trained healthcare professional, is the reference standard for assessing diagnostic accuracy) and ambulatory monitoring (Holter and/or event monitoring).
Outcomes	The outcome measures to consider include: System outcomes • Diagnostic yield and accuracy (sensitivity and specificity) • Atrial fibrillation burden, including the number of symptomatic and asymptomatic atrial fibrillation events detected during the recording period, and the time spent in atrial fibrillation • Time to detect first or recurrent atrial fibrillation events • Time to diagnosis or rule out of atrial fibrillation • Time to initiation of treatment (control symptoms and/or preventing the risk of future events) • Rate of test failure • Data transfer failure • Rate of fail to classify • Rate of secondary care referral • Total number of hospital outpatient appointments for investigation • Hospital admission • Number of outpatient visits and staff time for undertaking and analysing diagnostic tests • Number of visits to GP or urgent care • Number of further tests needs in addition to KardiaMobile • Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment) • Mortality Patient outcomes: • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction

	• Health-related quality of life • Device-related adverse events	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	• Adults referred for ambulatory ECG monitoring, who are symptomatic or asymptomatic • Adults referred for ambulatory ECG monitoring in primary care • Adults referred for ambulatory ECG monitoring in secondary care	
Special considerations, including those related to equality	KardiaMobile is not approved for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices. The device may not be suitable for people who cannot remain still or have problems holding the device; for example, people with tremor may have difficulty with recording an accurate trace. People are not able to use the device if they do not have a compatible smart device to access the KardiaMobile app. Age and disability are protected characteristics under the Equality Act. Full details of contraindications are listed the instructions for use for KardiaMobile.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	Cardiac arrhythmias can develop in people of any age but are more common in people over 60 years. The lifetime risk of developing atrial fibrillation is similar for both men and women, although it is slightly higher in men. Age and sex are protected characteristics under the Equality Act. People whose first language is not included in the app or who cannot read may not be able to communicate recorded information on their symptoms while using the KardiaMobile system. The app is	

	available in the following languages including English, German, Dutch, Spanish, French, Italian, Norwegian (Bokmål), Chinese (simplified or traditional), and Korean.

3 Related NICE guidance

Published

- Zio XT for detecting cardiac arrhythmias (2020) NICE medical technology guideline MTG 52.
- Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care (2019) NICE diagnostics guidance DG35.
- Atrial fibrillation: management (2014) NICE clinical guideline CG 180.
- WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension (2013) NICE medical technology guidance MTG 13.
- Transient loss of consciousness ('blackouts') in over 16s (2010) NICE clinical guidance CG 109. Last updated in 2014.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Academy for healthcare science
- British Association for Nursing Cardiovascular Care
- British Cardiovascular Society
- British Heart Rhythm Society
- Royal College of Emergency Medicine
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Society for Cardiological Science and Technology

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Arrhythmia Alliance
- Atrial Fibrillation Association
- Blood pressure UK
- British Cardiac Patients Association (BCPA)
- British Heart Foundation
- Cardiovascular Care Partnership
- Children's Heart Federation
- Down's Heart Group
- Heart Rhythm Alliance
- Heart UK
- Heart Valve voice
- Pumping Marvellous

NICE National Institute for Health and Care Excellence

Adoption report: GID-MT554 KardiaMobile for the ambulatory detection of atrial fibrillation

Summary

Adoption levers identified by contributors

- The ability to record ECGs over a number of weeks or months has the potential for greater diagnostic yield in paroxysmal atrial fibrillation, particularly when symptoms are infrequent or random.
- It can be used in primary care with appropriate pathways in place, reducing the number of people referred to secondary care.
- It has the ability to reduce attendance at healthcare settings as the monitor can be sent to the person and returned by post.
- It is cheap in comparison to alternative ambulatory monitors. It can be reused and has minimal maintenance requirements.
- It is easy to use with good acceptance.
- It is straightforward to adopt. Those who have adopted it report no major organisational, logistical or IT issues.

Adoption barriers identified by contributors

- It isn't continuous monitoring. It needs to be activated by the person, so it is unhelpful if they are incapacitated at the time of their symptoms (e.g. loss of consciousness).
- A minority of people cannot use the monitor as hands need to remain still to obtain a readable trace.
- It requires ECG interpretation skills, which may be additional training for non-specialists, such as those in primary care.
- Access to complementary technology is needed (for example, a smartphone or tablet which can connect wirelessly to the device), although users report this is becoming less of a barrier.
- There are potential information governance issues around emailing and sharing patient data, although this may be dependent on individual NHS settings.

1 Introduction

The adoption team has collated information from 7 healthcare professionals, 6 with experience of using KardiaMobile. This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC. It includes some of the adoption considerations for the routine NHS use of the technology.

2 Current practice in clinical area

All contributors acknowledged that currently, there is a gap in the investigation of people whose symptoms are suggestive of atrial fibrillation (AF), such as palpitations, but are infrequent and less than weekly. Arrythmias in this group may not be detected by a Holter monitor worn for up to 7 days, and the person may not be sufficiently high-risk or troubled by their symptoms to warrant undergoing an invasive procedure to place an implantable monitor. While this procedure is minimally invasive, it is expensive and can only be carried out in secondary or tertiary care.

Some contributors also stated that due to a lack of diagnostic capability in primary care, people presenting to their GPs with symptoms are commonly referred to secondary care for investigation and management. Some of these will be low risk (for example young people who are unlikely to have AF but need monitoring and reassurance, or those with possible AF but no other risk factors) and could be investigated and managed in primary care with robust clinical pathways in place, if appropriate equipment were available.

Some contributors also suggested there is a subset of people for whom continuous ambulatory monitoring via a Holter monitor would be desirable but may not be convenient or possible. For example, in rural areas where it is difficult for a person to attend a healthcare setting to have the monitor fitted and during COVID-19 when people were managed remotely if possible. Referral for a Holter monitor can also be associated with significant delays in some areas, which potentially leaves people with AF untreated and at higher risk of stroke.

3 Contributors and their use of KardiaMobile in practice

Details of contributing individuals and how they currently use KardiaMobile are listed in the below table.

Job title	Use of KardiaMobile
General practitioner in the NHS	Used in clinical practice in the NHS since 2015
Consultant cardiologist in the NHS	Not adopted
Senior cardiothoracic surgical pharmacist in the NHS	Used in pilot studies of screening since 2015
Arrythmia nurse specialist (non-NHS)	Used in clinical practice in a non-NHS setting since approx. 2017
Professor of cardiovascular nursing	Used in research studies on screening since 2010
Consultant cardiologist in the NHS	Used in clinical practice in non-NHS settings (private practice) since approx. 2016; intends to adopt into NHS practice
Consultant cardiologist in the NHS	Used in clinical practice in the NHS since 2015

The primary use of KardiaMobile by the contributors is in the investigation of suspected arrythmias, especially paroxysmal AF when symptoms are particularly infrequent or random. In this situation, they may replace the use of a Holter monitor, especially if symptoms occur less than weekly. It can also replace the use of an implantable event or loop recorder.

Many are also using it in people who have a confirmed diagnosis of AF which is being treated either pharmacologically or by ablation and requires monitoring to investigate ongoing symptoms, check AF recurrence, monitor rate or rhythm control or for reassurance.

One contributor reported using it in people who are due to be admitted for cardioversion, to ensure they were still in AF and appropriate for the procedure.

Some contributors are using KardiaMobile outside of the current scope of the guidance and report that its adaptability for purposes outside of ambulatory detection of AF is one of its benefits:

- Two contributors are using it exclusively in screening programmes although several others were aware of such programmes ongoing in their local areas.
- Two contributors are also using their own monitor opportunistically as a single time point test for arrythmia.
- Of those who had experience of using the 6 lead, they stated that they use it to assess and monitor for more complex arrhythmias where a single-lead ECG might be inconclusive, as well as AF.

Once someone has been identified as suitable for KardiaMobile monitoring, contributors reported that an arrythmia nurse specialist or cardiac technician or physiologist usually advises the person on how to use the monitor and if required, helps them to download the app. One contributor reported posting the monitor out to people during the COVID-19 pandemic and asking them to return it by post. No contributors had issues with monitors being returned.

People are asked to either email their ECGs when they experience symptoms, to email them in after a pre-defined period of time specified by their healthcare professional, or to bring the ECGs on their device to a follow up appointment. Emails are sent to a secure nhs.net address, usually set up for this purpose. This inbox may be direct to the person's healthcare professional or could be monitored by a cardiac physiologist, who then refers abnormal ECGs to the relevant healthcare professional.

4 Reported benefits

The potential benefits of adopting KardiaMobile, as reported to the adoption team by the healthcare professionals using the technology are:

- It offers the opportunity to record ECGs over a longer period time compared to commonly used ambulatory monitors. This may offer a greater diagnostic yield, particularly in paroxysmal AF when symptoms are infrequent or random. This could:
  - reduce the time to diagnosis allowing initiation of appropriate treatment and a consequent reduction in stroke risk.
  - provide reassurance for people for whom AF can be excluded.
- It can be used in primary care to reduce:

  - referrals to secondary care by either excluding AF or diagnosing and managing low risk people in a primary care setting.
  - stroke risk in high-risk individuals by diagnosing AF and potentially starting treatment whilst wating for a secondary care appointment.
- It could reduce unnecessary attendance at healthcare settings because:
  - the monitor can be sent to the person and returned by post.
  - the ECG can be emailed to the healthcare professional and a remote diagnosis made.
- It is cheaper to purchase than alternative ambulatory monitors commonly in use, such as Holter monitors and implantable loop recorders. It can be reused and has minimal maintenance requirements.
- It is non-invasive.

5 Insights from the NHS

Care pathway

KardiaMobile fits into the care pathway for the investigation of palpitations or other symptoms (excluding loss of consciousness) which could be due to AF. The method of ambulatory monitoring depends on the frequency, nature and severity of symptoms, as outlined in patient selection.

While patients can purchase the device directly, contributors working in the NHS preferred to procure their own supply to ensure appropriate patient selection. However, some contributors (both NHS and private) reported that where people want to purchase their own monitors for longer term monitoring, they were happy for them to do this.

Patient selection

Contributors agreed that appropriate patient selection is important for using this technology as existing methods of ambulatory monitoring are more suitable for some people. Continuous monitoring obtained via a Holter monitor provides valuable information which cannot be captured on a self-activated monitor. Contributors

identified the following groups of people as potentially suitable for using KardiaMobile:

- Those presenting with symptomatic episodes suggestive of AF, whose symptoms are unlikely to be picked up using 3-to-7-day continuous monitoring.
- Those diagnosed with AF who require monitoring post-treatment, to review rate or rhythm control, check for AF recurrence or provide reassurance.

Across these groups, the following factors were considered important:

- It is not suitable for those who are incapacitated at the time of their symptoms (for example, loss of consciousness or severely unwell) as it requires self-activation.
- Whether a clear trace can be obtained. Hands need to be kept still for at least 30 seconds and people with certain medical conditions (Parkinson's disease or some rheumatological conditions) or learning disabilities may struggle with this.
- Whether symptoms last for more than the minimum 30 seconds required to obtain the trace.

Clinician confidence and training

All users of KardiaMobile considered the ECG produced by the single-lead monitor adequate to provide an indication of possible AF and some contributors reported that they only review traces highlighted as 'abnormal' by the device. As healthcare professionals competent in interpreting ECGs, they generally don't rely on the algorithm classification or ignore it. The manufacturer advises in their product information that all interpretations should be reviewed by a medical professional for clinical decision-making.

It was suggested by contributors, including the GP, that not all non-specialists would be competent at interpreting ECGs and that appropriate training, robust pathways and adequate channels to a cardiology service for advice and guidance when required, would be needed for routine adoption in primary care.

Commissioning

NHS users of KardiaMobile reported that it is locally commissioned under routine processes for adopting new technologies. This includes submitting business plans and seeking approval from medical device committees. No contributors reported any specific barriers to it being adopted and commissioned locally. They reported that the cost of KardiaMobile is less than Holter monitors or implantable loop recorders. One user reported that he considered it to be cost-effective even when used as a single-use device, when compared to a Holter monitor.

Capacity

All contributors reported that training people to use KardiaMobile took less time than fitting and removing a Holter monitor. A Holter monitor needs to be set up and removed in a face-to-face appointment, where the KardiaMobile monitor can be posted followed by a virtual consultation. It can then be posted back to the service when no longer required. This has been particularly beneficial during the COVID pandemic.

Interpreting a KardiaMobile ECG takes less time than a Holter monitor, as it is a single trace of up to a few minutes, compared with a continuous trace over several days. The Holter trace is usually reviewed by a cardiac physiologist who needs to correlate it with the person's symptoms to produce a report. Whilst some contributors reported continuing to use a cardiac physiologist to triage all incoming KardiaMobile ECGs, others review the ECGs themselves at clinic appointments, removing the need for triage.

Governance

Other than using a secure email (such as nhs.net) and ensuring people are happy to send their data using personal email accounts, no contributor reported any information governance issues when adopting the technology within the NHS. One contributor suggested that as it is more common these days for people to receive information about their GP care via email, this is no longer a barrier. One contributor who is yet to adopt it in his NHS practice raised concerns that the IT department in his NHS trust may have issues with emailing personal data.

Most of the contributors were aware of KardiaPro, the paid-for web-based platform provided by the manufacturer for healthcare professionals to help facilitate transfer and review of ECGs. Other than those using the device for screening, none of them were currently using it. One contributor commented that they would consider using KardiaPro if the number of people using KardiaMobile in their service were to increase.

Patient experience

Once appropriate patient selection has taken place, all contributors reported high acceptance of the device. People are generally positive about being able to maintain some control over their condition and this has enhanced the patient-doctor relationship. All contributors stated that most people reported that it was easy to use.

NHS patients who are supplied with the monitor are expected to use their own device (smartphone or tablet) for storage of their ECGs via the Kardia app. Some services have considered supplying people with a compatible device but none have done this. Whilst access to a device with compatible software was raised as a barrier, most contributors reported this is becoming less of an issue. Some people have used use relatives or friends' phones to overcome this.

Maintenance

The monitor uses a 3V CR2016 coin cell battery. Some contributors reported having to change the battery, while others say this has never been needed and depends on how often the monitor is used. Some monitors have been in use for many years. All contributors were happy with longevity of the monitor and reported no maintenance issues.

Contributors reported no issues with cleaning the monitors for re-use with alcohol, following the same protocols for other similar items of reusable equipment.

6 Comparators

Most contributors had adopted KardiaMobile at a time when there were few other similar devices available, which restricted their choice. As more mobile ECG devices have become available, many people have purchased an alternative with no input

from their health care professional. The Apple Watch is widely used and three contributors said they were happy to use the ECG produced by this to aid a diagnosis of AF. One contributor reported that KardiaMobile had the advantage over similar technologies because of its ability to use cloud-based storage.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT551 KardiaMobile for the ambulatory detection of atrial fibrillation

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	AliveCor Ltd
Submission date	29/03/2021
Regulatory documents attached	Please list regulatory documents submitted (e.g., CE certificate, instructions for use, etc.)
Contains confidential information	No

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	Adults (18 years or older) with known or suspected atrial fibrillation are referred for ambulatory ECG monitoring by a clinician in primary, secondary, or tertiary care.	NA	NA
Intervention	The KardiaMobile system: KardiaMobile hardware (single-lead or 6 lead ECG monitor) and KardiaMobile app.	NA	NA
Comparator(s)	Current pathway for atrial fibrillation detection, which includes ECG (a 12-lead ECG, performed and interpreted by a trained healthcare professional, is the reference standard for assessing diagnostic accuracy) and ambulatory monitoring (Holter and/or event monitoring).	NA	NA
Outcomes	System outcomes • Diagnostic yield and accuracy (sensitivity and specificity) • Atrial fibrillation burden, including the number of symptomatic and asymptomatic atrial fibrillation events, detected during the recording period, and the time spent in atrial fibrillation	Only outcomes that were reported in the included clinical studies have been reported in this document	NA

	• Time to detect first or recurrent atrial fibrillation events • Time to diagnosis or rule out of atrial fibrillation • Time to initiation of treatment (control symptoms and/or preventing the risk of future events) • Rate of test failure • Data transfer failure • Rate of fail to classify • Rate of secondary care referral • Total number of hospital outpatient appointments for investigation • Hospital admission • Number of outpatient visits and staff time for undertaking and analysing diagnostic tests • Number of visits to GP or urgent care • Number of further tests needs in addition to KardiaMobile • Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment) • Mortality Patient outcomes: • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction		

	Health-related quality of life Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	NA	NA
Subgroups to be considered	Adults referred for ambulatory ECG monitoring, who are symptomatic or asymptomatic Adults referred for ambulatory ECG monitoring in primary care. Adults referred for ambulatory ECG monitoring in secondary care.	NA	NA
Special considerations, including issues related to equality	KardiaMobile is not approved for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators, or other	NA	NA

	implanted electronic devices. The device may not be suitable for people who cannot remain still or have problems holding the device; for example, people with tremor may have difficulty recording an accurate trace. People are not able to use the device if they do not have a compatible smart device to access the KardiaMobile app. Age and disability are protected characteristics under the Equality Act. Full details of contraindications are listed the instructions for use for KardiaMobile.		

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	KardiaMobile Single Lead / KardiaMobile 6 Lead / Kardia
Approved name	KardiaMobile / Kardia
CE mark class and date of authorisation	Class IIa 2015 KardiaMobile 2019 KardiaMobile6L

Version(s)	**Launched**	**Features**
Kardia App	2015	Mobile application
KardiaMobile	2015.	Single lead mobile ECG
KardiaMobile6L	August 2019	Six lead mobile ECG inclusive of lead i, II, III, aVR, aVL, aVF
Enter text.	Enter text.	Enter text.

Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Earlier diagnosis/detection of AF leading to improved patient outcome	(Goldenthal et al., 2019) (Hickey et al., 2017) (Reed et al., 2019) (Narasimha et al., 2018) (Haberman et al., 2015) (Bhavnani et al., 2018) (Yan et al., 2020)	KardiaMobile will lead to earlier diagnosis and initiation of treatment to control AF which could prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Improved identification of people with AF leading to an improved patient outcome	(Goldenthal et al., 2019) (Hickey et al., 2017) (Lowres et al., 2016) (Selder et al., 2019) (Reed et al., 2019) (Rajakariar et al., 2018) (Narasimha et al., 2018) (Tarakji et al., 2015) (Haberman et al., 2015) (Praus et al., 2021) (Reed et al., 2021) (Selder et al., 2020) (Treskes et al., 2020) (Lowres et al., 2020) (Yan et al., 2020) (Halcox et al., 2017) (Isma Nusrat Javed 2019) (Koh et al., 2019) (Dankers et al., 2019) (Bose et al., 2014) (Philip, 2016) (Soni et al., 2016) (Soni et al., 2019)	Improved identification of people with AF, could lead to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Improved patient compliance and data collection	(Hickey et al., 2017) (Lowres et al., 2016) (Reed et al., 2019) (Narasimha et al., 2018) (Tarakji et al., 2015) (Haberman et al., 2015)	Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	(William et al., 2018) (Hermans et al., 1920) (Praus et al., 2021) (Treskes et al., 2020) (Magnani et al., 2017) (Lowres et al., 2020) (Halcox et al., 2017) (Saxon et al., 2012) (Bose et al., 2014) (Reading et al., 2017)	Little if any preparation is required for patients using the device so ECG recordings are simple, painless, and do not impact QOL.
System benefits		
"Improved diagnostic yield, minimizing the number of repeat tests needed to confirm or rule out AF".	(Narasimha et al., 2018) (Yan et al., 2020)	"Improved diagnostic yield, minimizing the number of repeat tests needed to confirm or rule out arrhythmia".
Improved diagnostic accuracy and efficiency in detecting AF in symptomatic and asymptomatic patients.	(Goldenthal et al., 2019) (Lowres et al., 2016) (Selder et al., 2019) (Reed et al., 2019) (Rajakariar et al., 2018) (Narasimha et al., 2018) (Tarakji et al., 2015) (Haberman et al., 2015) (William et al., 2018) (Hermans et al., 1920) (Selder et al., 2020) (Wasserlauf et al., 2019) (Karregat et al., 2020) (Isma Nusrat Javed 2019) (Koh et al., 2019) (Grieten et al., 2017) (Dankers et al., 2019) (Goel et al., 2018)	Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure.
Avoiding unnecessary referral to secondary care.	(Goldenthal et al., 2019)	Avoiding unnecessary referral to secondary care could lead to cost savings
Ease of implementation; minimal changes in facilities or	(Reed et al., 2019)	Ease of implementation;

infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.	(Narasimha et al., 2018) (Haberman et al., 2015) (Praus et al., 2021) (Reed et al., 2021) (Soni et al., 2016) (Soni et al., 2019)	minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.
Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway	(Goldenthal et al., 2019) (Praus et al., 2021) (Bhavnani et al., 2018) (Soni et al., 2016) (Soni et al., 2019)	Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduce the in-clinic analysis of ECG recordings and reduced outpatient appointments.
Cost benefits		
Reduction in costs and resource use.	(Goldenthal et al., 2019) (Reed et al., 2019) (Narasimha et al., 2018) (Praus et al., 2021) (Bhavnani et al., 2018)	Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure.
Sustainability benefits		
Cardiovascular Disease has a great impact on patients being able to live independently. As this disease worsens, it leads to regular visits to the hospital that involves accompanied travel. While these patients are admitted to the hospital, they use lots of resources to care for them, including electricity, water, lighting, medical consumables,	Enter text.	Enter text.

and staff to care for them. These staffs need to travel. Preventing CVD leads to a reduction of hospital visits and resources, travel costs leading to Co2 reduction. The benefits of a technology that helps to diagnose serious conditions early, lead to patients being able to live independently and normally, leading to the ability to exercise regularly and be able to walk and cycle, for example, leading to a reduction in C02.		

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

KardiaMobile (AliveCor) is a portable Single-lead or Six-lead electrocardiogram (ECG) recorder to monitor patient ECGs and to detect cardiac arrhythmias. The devices work with a compatible mobile device (such as a smartphone or tablet) running the Kardia app, which is intended to be used for analysing the ECG recording and sending it to a healthcare professional for interpretation.

KardiaMobile is available as a single-lead or as a 6-lead (KardiaMobile 6L) ECG recorder. The single-lead version has 2 electrodes on the top surface; 2 fingers from the left hand are placed onto 1 electrode and 2 fingers from the right hand are placed onto the other electrode. KardiaMobile 6L has 3 electrodes; 2 electrodes on the top surface (for 2 fingers from each hand), and one on the bottom which is placed on the left leg.

KardiaMobile is intended to replace or enhance the current assessment pathway for cardiac arrhythmia detection in adult patients referred for ambulatory ECG monitoring, palpitations, suspected cardiac arrhythmia such as AF or Post AF / Flutter treatment monitoring (e.g., Post Ablation/cardioversion/ cardiac surgery). The KardiaMobile devices are not restricted by the length of time in which they can be used to monitor a patient.

People must keep their arms still and must keep touching the electrodes for at least 30 seconds for a complete reading to be taken. The app has an option for either single-lead or 6-lead ECG reading. The default length of recording is 30 seconds; however, this can be extended up to 5 minutes. The company recommends that recordings are taken daily, or whenever arrhythmia symptoms are experienced. A user may also be given specific advice by their physician on how often to use the device and in-app reminders can be set.

Internet access is not needed when taking the reading. While KardiaMobile is taking a reading, it is sent wirelessly (via high-frequency sound waves for KardiaMobile Single lead and via Bluetooth Low Energy for KardiaMobile6L) to the mobile device, where it can be viewed in the Kardia app. The app works on devices running Apple or Android operating systems (a full list is available on the compatibility section of the company's website). It shows the ECG trace, a measure of heart rate, and determinations of the rhythm, the possible determinations are Normal, Possible AF, Tachycardia, Bradycardia, Premature Ventricular Contractions (PVCs), Sinus Rhythm with Supraventricular Ectopy (SVE), Sinus Rhythm with wide QRS or Unclassified. It saves and analyses data from the monitor. Patient information, such as name and NHS number, can be added to the recording following information governance and the general data protection regulations (GDPR). When the device has a Wi-Fi or mobile connection, the recording automatically synchronizes with a secure encrypted cloud server. Storage can be turned off manually from the device (to support GDPR). An optional extra for healthcare professionals is the KardiaPro software, which allows remote monitoring of Kardia users and generation of reports.

KardiaMobile is not intended for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators, or other implanted electronic devices. The company states that the ECG recorded by KardiaMobile is used to help diagnose heart rhythm

disturbances but is not intended to be used to diagnose other cardiac conditions. The findings should be reviewed by a medical professional and used to support clinical decision-making.

The expected service life of the single-lead and 6 lead devices is 2 years. The technology has previously been known as AliveCor Heart Monitor and AliveCor Mobile ECG. A smartwatch band, Kardiaband, has been discontinued.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Cardiovascular Disease has a great impact on patients being able to live independently. As this disease worsens, it leads to regular visits to the hospital that involves accompanied travel.

While these patients are admitted to the hospital, they use lots of resources to care for them, including electricity, water, lighting, medical consumables, and staff to care for them, and these staffs need to travel.

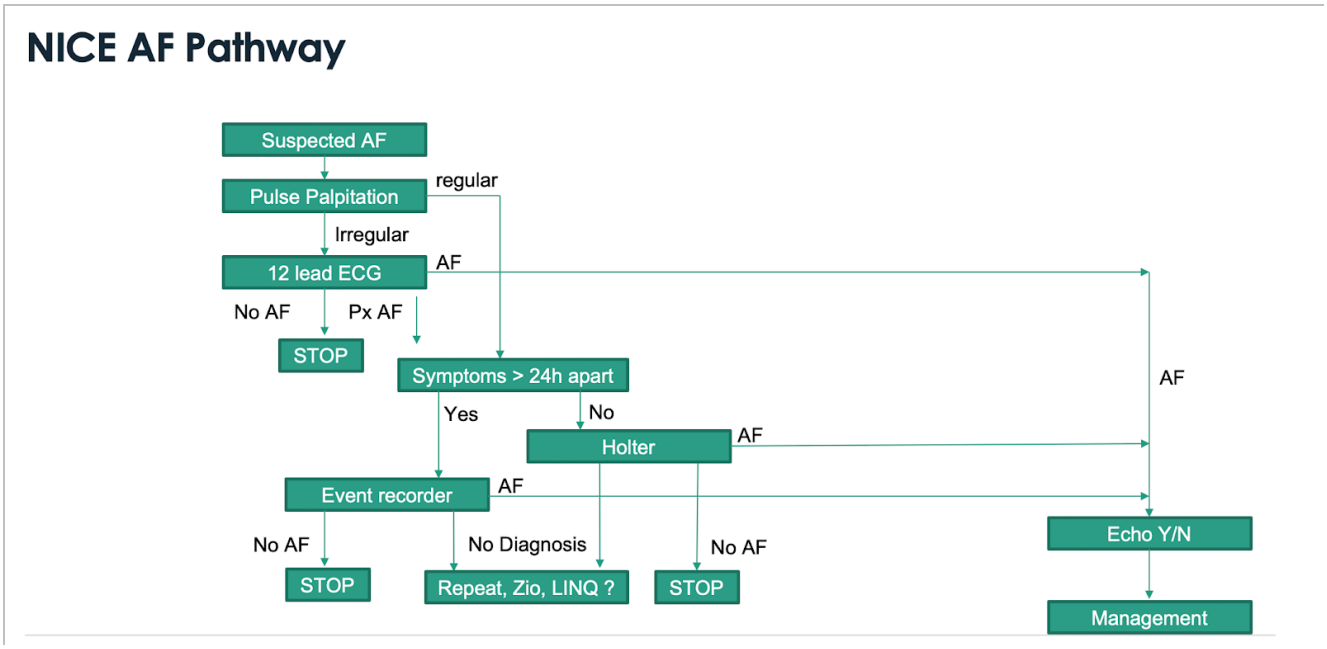
Preventing CVD leads to a reduction of hospital visits and resources, travel costs leading to Co2 reduction.

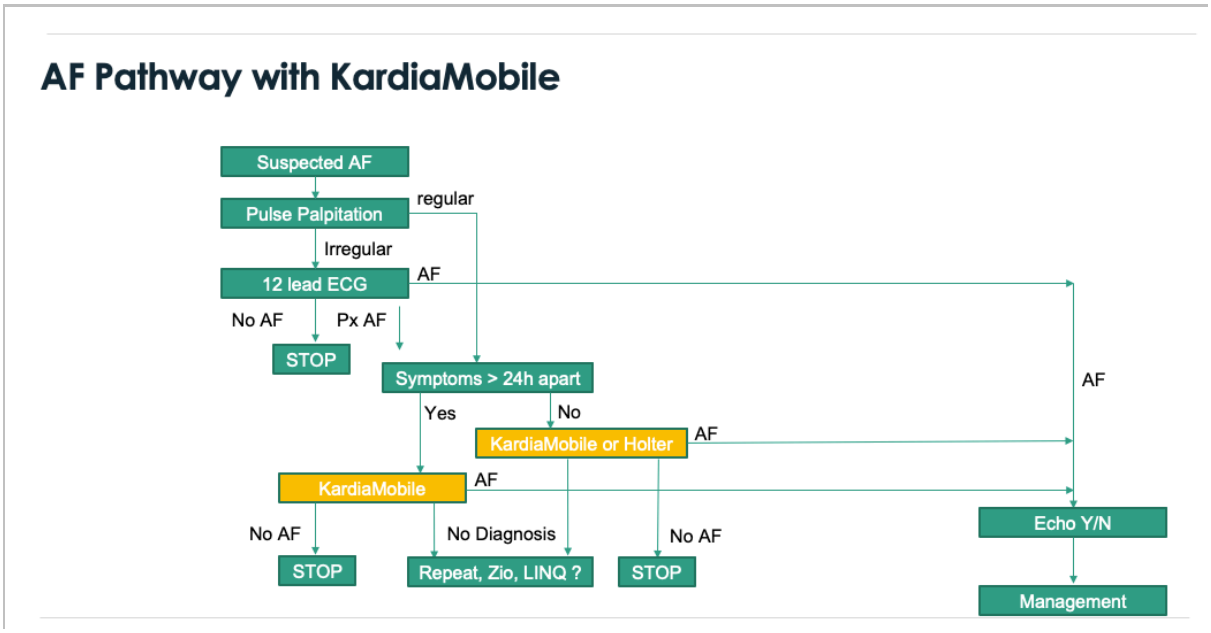
The benefits of a technology that helps to diagnose serious conditions early, lead to patients being able to live independently and normally, leading to the ability to exercise regularly and be able to walk and cycle, for example, leading to a reduction in C02.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

https://pathways.nice.org.uk/pathways/atrial-fibrillation#path=view%3A/pathways/atrial-fibrillation/assessing-atrial-fibrillation.xml&content=view-node%3Anodes-electrocardiography





Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

All training is available within the Kardia Application, virtual training of Kardia application and device usage is also available on request for health care professionals by AliveCor. Once the application is downloaded and an account is set up, the application walks through how to use the KardiaMobile device, how to navigate the application and how to take an accurate ECG.

User videos are available describing how to take an ECG from the below links
https://vimeo.com/335613884
https://vimeo.com/251698484

User Videos and images are also available and presented within the app at setup. A quick setup and user training guide is also available please see attached (attach user guide)

Additional support can be found on our website https://AliveCor.zendesk.com/hc/en-us/articles/1500000111761
Technical support is available from AliveCor also contact details are below.
Customer support line: +44 (0) 333 301 0433
Email: uksupport@AliveCor.com

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		1533
Number of studies identified as being relevant to the decision problem.		44
Of the relevant studies identified:	Number of published studies (included in table 1).	24
	Number of abstracts (included in table 2).	9
	Number of ongoing studies (included in table 3).	15

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Recurrent atrial fibrillation/ flutter detection after ablation or cardioversion using the AliveCor KardiaMobile device: iHEART results (Goldenthal et al., 2019)	**Author**: Goldenthal et al. **Year**: 2019 **Location**: United States of America	A Randomized Control Trial	- **Inclusion criteria**: patients undergoing catheter radiofrequency ablation (RFA) or direct current cardioversion (DCCV) for AF/AFL: age 18 and older and history of documented AF and at least one AF risk factor (including sedentary lifestyle, obesity, hypertension, smoking, and diabetes) - **Exclusion criteria**: a history of cognitive impairment, unwilling to have their clinical data collected, unwilling to receive text messages.	Patients were randomized to the iHEART intervention. The intervention is **AliveCor KardiaMobile** ECG monitor for 6 months. ECG was recorded and analysed using KardiaMobile once per day, plus when symptoms happened (n=115).	**Standard care** (n=123, follow-up not obtained in 5 patients)	1-Documented rate of recurrence in the control group. 2-Documented rate of recurrence in the intervention group. 3-The likelihood of recurrence detection in the control vs intervention group. 4-Rate of treatments of recurrence in the control group. 5-Rate of treatments of recurrence in the intervention group. 6-The likelihood of taking treatment in recurrences in the intervention group vs those in the control group. 7-All cause hospitalization and room visit between two groups.

			- **withdrawals/lost to follow up**: A total of seven patients (six control and one intervention) were not included because the follow-up period started immediately post-procedure. Two patients were not randomized because they did not convert to sinus rhythm by DCCV. Five (one control and four intervention) withdrew from the study. Ten patients randomized to the intervention were discharged without being set up to connect to the Kardia portal to enable ECG transmission and were also excluded. **Total population:**			

			- Intervention group: n=115 - Control group: n=123 **Age (mean + SD), y:** - Intervention group: 61 + 12 - Control group: 61 + 12 **Males**: - Intervention group: 88/115 (77) - Control group: 96/123 (78) - **Comorbidities**: Hx of stroke/TIA: Intervention 11/115 (10%) Controls: 10/123 (8%) Hx of congestive heart failure: Intervention 22/115 (19%) Controls: 26/123 (26%)			
Evaluating the Utility of Mhealth ECG Heart Monitoring for the Detection and	**Author**: Kathleen T. Hickey et al,	A pilot case-control study	- **Inclusion**: 21 years or older, with a documented	**KardiaMobile** once per day, plus when	**Standard care** (usual cardiac medical care: no	1-AF detection rate in the intervention group

Management of Atrial Fibrillation in Clinical Practice (Hickey et al., 2017)	**Year**: 2017 **Location**: United States of America		history of AF. Control group of age (within 5 years) and gender-matched patients. **Total population:** - Intervention group: n=23 - Control group: n=23 - **Age** (mean + SD), y: Intervention group: 55 ± 10 Control group: 55 ± 9 - **Males**: - Intervention group: 15 (71%) - Control group: 15 (71%) - **Comorbidities**: Previous Cardioversion: Intervention:16 (70%) Control:13 (57%) Cardiac Ablation Intervention:10	symptoms happened. (given a heart monitor (AliveCor™)	daily ECG self-monitoring)	2- AF detection rate in the control group 3-Difference between detection rate of two groups 4-Improvement of Quality-of-life assessment within 5 months. 5-Patients compliance with device usage.

			(43%) Control:11 (48%) Coronary Artery Disease: Intervention:3 (13%) Control:3 (13%) Stroke/TIA Intervention:3 (13%) Control:0 (0%) Congestive Heart Failure: Intervention 6 (26%) Control:3 (13%) CHA2DS2-VASc > 1 Intervention:5 (22%) Control:3 (13%) Diabetes: Intervention:1 (4%) Control:3 (13%) - Hypertension: Intervention:11 (48%) Control:13 (57%)			
Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone	**Author:** Nicole Lowres et al **Year**: 2016	A cross-sectional cohort–feasibility study	- **Inclusion**: cardiothoracic surgery patients who experienced a transient episode of postoperative AF	**AliveCor heart monitor** record a 30-s iECG four times a day during the study period and take additional iECGs if AF	Noun/unclear	1-Detection of AF recurrence 2-The number of traced records

electrocardiogram (Lowres et al., 2016)	**Location**: Australia		following cardiac surgery; with no history of AF before admission; who reverted or were cardioverter to stable sinus rhythm prior to discharge; and were ≥18 years old. - **Exclusion**: Not eligible: History of AF, discharged in AF, unconfirmed AF, non-English speaker, impaired cognition, pacemaker inserted. Not appropriate: vision impairment, long hospital stay, CVA/ neurorehab, mental illness. **Design**: - All participants received the intervention. - All participants received brief one-on-one	symptoms were experienced. Reviewed by a Research Assistant, and analysed by a validated algorithm for the presence of AF		3-The detection accuracy of the device 4-The usability of the device 5-Association of false-positive iECGs. 6-The detection rate of AF after discharge 7-Any associations between AF recurrence and age group, gender, or AF risk factors.

			education regarding AF and were also provided with an iPhone and an AliveCor Heart monitor (iECG) - AF knowledge assessed before and after the education. - **withdrawals/lost to follow up**: - 14 (24%) of the 58 patients approached declined participation, the majority of those who refused to state they were feeling too overwhelmed post-surgery to participate in a research study. 9 out of 14 were women. - **Total population:** - 44 participants were recruited. Of the 44 participants:			

			Died during in-patient stay n=1 Withdrew=1 - 42 completed the intervention. 40 final assessment and interview			
A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs (Selder et al., 2019)	**Author**: J. L. Selder et al. **Year:** 2019 **Location**: the Netherlands	Diagnostic accuracy study (cross-sectional)	**Inclusion**: The study population consisted of all Hartwacht Arrhythmia (HA) patients, who submitted a Kardia Mobile (KM) ECG from the start of the program in January 2017 until March 2018. Patients presenting with paroxysmal AF, palpitations of unknown origin, or near-collapse were selected by the cardiologists of this clinic to participate in the Hartwacht program. After inclusion in the HA program, participants received the KM. **Total Participants:**	Index test (intervention): ECG recorded and analysed using **KardiaMobile** when symptoms happened. (KM algorithm)	Reference standard: Using the assessment of the Hartwacht team as the reference standard (**cardiologist interpretation**).	1-Number of ECGs per patient per month and time of day that ECGs were received. 2-Classification of the ECG by the KM algorithm and results of the assessment by the Hartwacht team. 3-Number of ECG classifies by KM algorithm as one of four categories: (a) normal sinus rhythm, (b) possible AF, (c) unclassified, or (d) unreadable. 4-Algorithm interpretation agreement between two devices. 5-Performance of devices for detection of AF and other abnormalities.

			N= 233 Seven patients (3%) exited the program, mostly because they never made ECGs. **age**: 58.4 (±14) **male**: 120 (52%)			
The IPED (Investigation of Palpitations in the ED) Study: Multi-center Randomized Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED (Investigation of Palpitations in the ED) study (Reed et al., 2019)	**Author:** Matthew J. Reed, **Year:** 2019 **Location: UK** participants were recruited to the study at 10 centres (Edinburgh 66 participants, 27.2%, Reading 57, 23.5%, Royal London 43, 17.7%, Exeter 24, 9.9%, Plymouth 15, 6.2%,	Multi-center-open label Randomized Controlled Trial	**-Total N=243** -Allocated to Control arm (n =117) -Allocated to Intervention arm (n =126) **-Age in years/mean (SD):** -Intervention: 40.0 (14.0) -Control: 39.1 (13.5) **-Male: N=105** **-To be included:** Participants aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG	standard care **plus** the use of a smartphone-based event recorder, **AliveCor** Heart Monitor	**Standard care** 24-hour **Holter** 48-hour Holter 7+ day Holter Subsequent ED visit ECG GP visit ECG	1-detection of symptomatic rhythm in intervention and control group 2- detection of symptomatic cardiac arrhythmia in intervention and control group 3- the time of the detection of symptomatic rhythm 4- the time of the detection of cardiac arrhythmia 5- types of symptomatic cardiac arrhythmia

	Chesterfield 12, 4.9%, Leicester 12, 4.9%, Musgrove Park 5, 2.1%, Nottingham 5, 2.1%, Whipps Cross 4, 1.6%).		rhythm during these episodes remains undiagnosed after ED(Emergency Department) assessment **-Exclusion:** One participant was removed from the study by the local study team after being randomized, as they did not meet the inclusion criteria			6- Rate of serious outcomes in two groups. 7-number of patients undergoing treatment. 8-Emergency department (ED) presentations within two groups.
Modified positioning of a smartphone-based single-lead electrocardiogram device improves detection of atrial flutter(Rajakariar et al., 2018)	**Authors:** Kevin Rajakariar, Anoop N. Koshy et al. **Year**: 2018, **Location**: Australia	prospective, multi-center blinded validation study as performed at three tertiary university hospitals	**Inclusion:** -A total of 55 consecutive patients ≥18 years of age on continuous cardiac monitoring were invited to participate in over 6 months of screening. **Exclusion:** Patients with cardiac implantable electronic devices, in contact isolation or those unable to hold the device correctly due to physical limitations or significant tremors, were excluded. 5 patients were excluded as they did	AliveCor Kardia	A 12-Lead ECG	1-the number of recording ECGs 2-Types of the recorded trace 3-the sensitivity of AF detection by EP(ElectroPhysiologists) 4-the sensitivity of AFL detection by clinicians 5-the Sensitivity of modified position 6-Types of diagnosed abnormalities.

			not fulfil inclusion criteria (significant tremor [n = 2], implanted cardiac device [n = 2], contact isolation [n = 1]). **-Total eligible population:** 50 patients (74.1±14.8 years of age) eligible for inclusion into the study.			
Validation of a smartphone-based event recorder for arrhythmia detection(Narasimha et al., 2018)	**Author**: Deepika Narasimha et al. **Year**: 2018, **Location**: USA	Prospective validation study	**Total population**: N=38 -ITT (Intension to treat) sample: N=38 -PP (Per protocol) sample: N=33 -**Age:(Mean SD)** = 47.5 (13.8) -only 33 patients had monitoring data for both devices. Of the five patients who did not have complete data, two discontinued the use of the ELR after one day of use (citing a	**AliveCor Kardia mobile**	**external loop recorders (ELRs),** (Lifewatch, Rosemont, IL, USA)	1-The number of the recorded trace 2-types of tracing records 3-device compliance by patients 4-comparison of patients' compliance between groups 5-The detection rate of the device 6-the device yield of detection.

			skin allergy to the electrodes and cumbersomeness of the ELR) and three patients did not send an initial rhythm strip from the KM device to start transmitting data. **Withdrawals:** only one patient was deemed unsuitable for inclusion in the study, as he suffered from Parkinson's disease and had resting tremors that would preclude him from recording good rhythm strips from the KM device. **Inclusion criteria:** -patients≥18yearsof age with palpitations (usually occurring less frequently than once a day) with prior non-diagnostic ECGs and/or Holter monitoring who demonstrated the ability to use a smartphone device to record and upload			

			a test ECG recording at the office visit. **Exclusion criteria** : -myocardial infarction within the last3 months, known history of sustained ventricular tachycardia (VT)/fibrillation, New York Heart Association class IV heart failure, unstable angina, syncope as the presenting symptom, inability or unwillingness to use the device, and movement disorders including but not restricted to tremors. -The detection rate was defined as the percentage of days in which at least one diagnostic recording (i.e., symptomatic arrhythmia) was made during the monitoring period for each patient. -The diagnostic yield is (percentage of			

			patients with detected symptomatic or asymptomatic arrhythmias).			
Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: The iTransmit study(Tarakji et al., 2015)	**Author:** Khaldoun G. Tarakji et al. Year: 2015 **Location**: the USA	a single tertiary center, nonrandomized, single-blinded study	**Total Population**: N=60 only 55 patients completed the study (1 patient urgently traveled overseas, 1 broke his phone and purchased a different brand, and 3 patients withdrew their consents) **Age (mean, SD)**: N=60+-12 -Patients undergoing AF ablation with or without atrial flutter ablation who had iPhone 4, 4S, or 5 were screened for enrolment. **Inclusion criteria:** included male or female patients, Z18 and r75 years old, history of paroxysmal or	**AliveCor heart monitor (AHM)**	traditional transtelephonic monitor (TTM), transmitted to a **Holter** (Pacetrack, Mednet Healthcare Technologies, Inc, Ewing, NJ, or CarryAll EZ Monitor, Instromedix, San Diego, CA)	1-the number of tracing records 2-types of recordings 3- detection rate of the device 4-the performance and sensitivity of the device 5-patients compliance for using the device.

			persistent AF, scheduled to undergo an AF ablation procedure, already had iPhone 4, 4S, or 5 with a data plan, and were willing to use the AHM. **Exclusion criteria:** excluded patients who were unwilling or unable to use their phones and those residing outside the United States.			
Wireless Smartphone ECG Enables Large-Scale Screening in Diverse Populations (Haberman et al., 2015)	Author: ZACHARY C. HABERMAN, Year: 2015 **Location**: USA The study population consisted of 123 the University of Southern California, (USC) Division I Athletes, 128	Observational / Case-control	**Total Study Population:** N=381 **Age**(years+-SD): 35+-20 **-Division I Athletes** N=123 **Age**(years+-SD): 19+-1 **-Healthy Young Adults:** N=128 Age(years+-SD):	**The AliveCor device**	**Standard 12lead ECGs**	1-the sensitivity of device for 3 groups within the study 2-patients compliance for using the device

	asymptomatic USC students, and 130 ambulatory USC cardiology clinic patients.		25+-2 **Cardiology Clinic Patients:** N=130 Age(years+-SD): 59+-15			
Assessing the accuracy of an automated atrial fibrillation detection algorithm using smartphone technology: The iREAD Study (William et al., 2018)	**Author:** Amila D. William, 2018 **Location:** USA	a single-center, nonrandomized, and adjudicator-blinded study	**Total population:** 52 patients **Age, average (min-max) (y):** 68.1 (42.6–85.6) **Design**: Patients with a diagnosis of AF who were admitted for antiarrhythmic drug initiation (dofetilide or sotalol) were screened for enrolment. **Inclusion criteria:** included male or female patients, aged 35–85 years with a history of paroxysmal or persistent AF, with baseline corrected QT interval less than 470 or 500 ms if the	**The Kardia Mobile** Cardiac Monitor (KMCM; AliveCor, Mountain View, CA)	**12-lead ECG**	1-the number of tracing records 2-the sensitivity and specificity of the device 3-the physician interpreting sensitivity of the device 4- the patient's compliance for using the device.

			QRS duration was greater than 120 ms. **Exclusion criteria:** Patients with pacemakers or defibrillators were excluded.			
Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation(Hermans et al., 2021)	**Author:** Hermans, A. N. L. **Year:** 2021 **Location:** The Netherlands	a prospective observational cohort study	Total population=115 Included in study = 115 The monitoring strategies (Holter and ACK) were evaluated at 3months follow-up in 74 patients (64.3%), at 6 months follow-up in 16 patients (13.9%), and at 12 months follow-up in 25 patients (21.7%). **Inclusion:** Patients (≥18 years) who underwent paroxysmal AF ablation from May 2017 to October 2019 in the Maastricht University Medical Centre, TheNetherlands, were included in this study.	ACK = AliveCor device	Holter 24H	1-the difference in the proportion of patients with AF recurrences detected by long-term intermittent heart rhythm monitoring using ACK compared to short continuous heart rhythm monitoring using Holter. 2-the usability and user-friendliness of both long-term intermittent heart rhythm monitoring by ACK and short continuous heart rhythm monitoring by Holter 3-the correlation between clinical/demographic variables and long-term intermittent heart rhythm recordings transmission with ACK 4-the sensitivity and specificity of the ACK

			Exclusion: Individuals were excluded if they had no smartphone and were not able to operate the ACK system after instructions. Additionally, just a limited number of ACK devices were available, which was a limiting factor in the inclusion of patients.			algorithm for AF detection
Improving care for patients with atrial fibrillation through the use of a personal electrocardiogram (Praus et al., 2021)	**Author:** Praus, T. **Year:** 2021 **Location:** USA	Observational, Cohort	**Total population:** **43 Patients** **Eligibility criteria included:** adult patients who (1) had two or more AF-related ED or UC visits in the past 12 months, (2) needed rate control with medication titration, or (3) needed monitoring for AF reoccurrence after re-establishing sinus rhythm—either by chemical or direct current cardioversion. Additionally, participants needed	KardiaMobile (KM)	None	1- the impact of providing patients with a personal single-lead ECG and telehealth access and Outcomes of AF-related resource utilization. 2-the patient's level of anxiety 3-patient satisfaction with care and access

			to be established with the clinic, able to understand and consent to participate, and have comfort using the personal ECG device and application on their smartphone. Forty-three patients were identified and participated in the project.			
Establishing a Smartphone Ambulatory ECG Service for Patients Presenting to the Emergency Department with Pre-Syncope and Palpitations (Reed et al., 2021)	**Author:** Matthew J. Reed **Year:** 2021 **Location:** UK	Observational/Cross-sectional	**Total population:** **68 patients** **Inclusion criteria:** patients aged 16 years or older presenting to the ED(Emergency Department) or Acute Medicine Unit (AMU) of the Royal Infirmary of Edinburgh (RIE) with palpitations or pre-syncope, whose ECG was normal, who had a compatible Apple/android phone, tablet, or watch, and in whom an underlying cardiac dysrhythmia	Kardia mobile	None	-Detection rate of symptomatic cardiac dysrhythmia -Types of detected arrhythmia

			was possible, was offered an appointment at the SPACC, which was based in an ambulatory care clinic setting beside the ED. Exclusion: The patient being non-ambulant, requiring hospital admission, having a prior diagnostic ECG, having multiple frequent episodes or recent acute myocardial infarction (AMI), severe heart failure, or unstable angina, having associated chest pain or syncope, being unwilling or unable to use the AliveCor Heart Monitor and ECG App, having a cardiac pacemaker or other implanted electronic device, or having a likely non-cardiac cause for their palpitations (e.g., anxiety, sepsis).			

Assessment of a standalone photoplethysmography (PPG) algorithm for detection of atrial fibrillation on wristband-derived data (Selder et al., 2020)	**Author:** Selder, J. L. **Year:** 2020 **Location**: Belgium	An observational, prospective cohort study	**Total population: 60 Patients** **Exclusion criteria :** were age < 18 years and pacemaker dependent rhythm.	the Wavelet wristband (Wavelet Health, California, US) on one arm	a one-lead-ECG device (the AliveCor Kardia Band, AliveCor, on the other Arm	1-The detection rate of AF 2-Diagnostic performance of both devices
Effect of Smartphone-Enabled Health Monitoring Devices vs Regular Follow-up on Blood Pressure Control Among Patients After Myocardial Infarction (Treskes et al., 2020)	**Author:** Treskes RW **Year:** 2020 **Location:** The Netherlands	RCT	**Total population** =200 patients Design: Patients were randomized in a 1:1 fashion between a smart technology intervention ("The Box") and regular follow-up. Withdraw: 24 patients did not reach the 1-year follow-up. Four patients died: Twenty patients were lost to follow-up. **Reason for withdrawing:** the fear that they would be confronted with their disease too often, fear of not	a single-lead ECG device (Kardia; AliveCor Inc).	10- second 12-lead electrocardiogram (ECG),	1-proportion of patients with controlled BP after 1 year of follow-up. 2-Patient satisfaction and acceptance regarding the intervention 3-feasibility of E-device

			being able to cope with technology, wanting to be followed-up in a different hospital, and refusing to give a reason or another reason for not participating.			
Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation (Wasserlauf et al., 2019)	**Author:** Wasserlauf, J. **Year:** 2019 **Location:** USA	Observational cohort	Total population: 26 patients 2 were excluded for demonstrating >50% of ICM-detected AF episodes that were not due to AF as adjudicated by available electrograms. Additionally, a complete list of AF episodes was not available for these 2 patients due to a high number of FP episodes that exceeded the memory of the ICM. Inclusion: Patients with previously implanted ICMs (Reveal LINQ; Medtronic Inc, Minneapolis, MN) and a history of paroxysmal AF were	Kardiaband-AliveCor (AF-sensing watch/AFSW)	an insertable cardiac monitor (ICM; Reveal LINQ).	1-Detection rate of AF 2-sensitivity of the AFSW for AF episodes ≥1 hour. 3-sensitivity of the AFSW for detection of AF by subject and sensitivity for total AF duration across all subjects.

			eligible for enrolment. Exclusion: Subjects with >50% false-positive AF episodes on ICM were excluded.			
The Atrial Fibrillation Health Literacy Information Technology System: Pilot Assessment (Magnani et al., 2017)	**Author:** Magnani, J. W. **Year:** 2017 **Location:** Pittsburgh	RCT	**Total population:** **31 participants** **Inclusion criteria**: included adult (age ≥18), a diagnosis of non-valvular AF as ascertained by review of the electronic health record, CHA2 DS2-VASc score ≥2, and receiving oral anticoagulation. **Exclusion:** Participants were excluded for having an identified extracardiac cause of AF (such as sepsis or thyroid disease), as the management of AF in such context may differ based upon the underlying aetiology; inability to provide accurate three-word	Combination of a smartphone-based relational agent and Kardia system	None	1-mean number of days using Alivrcor. 2-Improvement of the AFEQT (Atrial Fibrillation Effect on Quality of life) 3-Improvement of self-reported medication adherence 4-Acceptability of device

			recall; inability to provide informed consent; or being non-English speaking.			
A Randomized Trial of Pocket-Echocardiography Integrated Mobile Health Device Assessments in Modern Structural Heart Disease Clinics (Bhavnani et al., 2018)	**Author:** Sanjeev P. Bhavnani, **Year:** 2016 **Location:** India	RCT	**Total population:** **253 subjects** mHealth Arm: 139 patients Standard care: 114 patients **Inclusion criteria:** to include SHD patients with a prior valvuloplasty or valve replacement. **Exclusions**: included neonatal patients and those with an unstable hemodynamic status.	AliveCor	Standard care: 12-lead ECG	1- the time to treatment with valvuloplasty or valve replacement over 12-months after the initial mHealth or standard-care assessment. 2- the occurrence of cardiovascular hospitalization and/or death on follow-up.
Evaluation of general practitioners' single-lead electrocardiogram interpretation skills: a case-vignette study (Karregat et al., 2020)	**Author:** Karregat, E. P. M. **Year:** 2020 **Location:** The Netherlands	Online case-vignette study	Invited 2239 Dutch GPs for an online case-vignette study. GPs were asked to interpret four 1L-ECGs, randomly drawn from a pool of 80 case-vignettes. These vignettes were obtained from a primary care study that used smartphone-	KardiaMobile	Standard care: 12-lead ECG	1-Kardia Device performance assessed by General practitioner for detection of AF. 2-Kardia Device performance assessed by General practitioner for detection of any relevant abnormalities.

			operated 1L-ECG recordings using the AliveCor KardiaMobile. Interpretation of all 1L-ECGs by a panel of cardiologists was used as a reference standard. A total of 457(20.4%) GPs responded.			3-GPs diagnostic performance
Self-monitoring for recurrence of secondary atrial fibrillation following non-cardiac surgery or acute illness: A pilot study (Lowres et al., 2020)	**Author:** Lowres N **Year:** 2020 **Location:** Australia	A prospective feasibility study / cross-sectional	**Total screened population:** 16,454 patients Ninety-four of the 224 secondary AF patients (42%) were eligible for recruitment, The study recruited patients with an episode of new-onset AF secondary to hospitalization for either non-cardiac surgery or non-cardiovascular acute medical illness. **Inclusion**: Patients were eligible if they were 1) admitted to	AliveCor KardiaMobile ECG	None	1- acceptability and patient willingness to participate in the program (measured using recruitment data and qualitative process evaluation) 2- compliance of participants to the intervention (measured by the number of actual ECG recordings compared to a requested protocol, and if participants actioned a review with their treating doctors if 'possible AF' was diagnosed by the on-device automated algorithm) 3- the incidence of AF recurrence identified

			hospital in sinus rhythm with no prior history of AF; 2) reverted to sinus rhythm before discharge (spontaneously or via cardioversion); 3)! 18 years; 4) able to provide informed consent. **Exclusion**: Patients were excluded if they were non-English speaking or were unable to be contacted by phone following discharge.			through self-monitoring after discharge
Nurse Led Smartphone Electrographic Monitoring for Atrial Fibrillation after Ischemic Stroke: SPOT-AF(Yan et al., 2020)	**Author:** Yan B **Year:** 2020 **Location:** Australia and china	a pragmatic observational, multi-center study	**Total population:** **1079 participants** Of the 294 patients who underwent both 24-hour Holter and iECG monitoring, two did not provide their age, and five had missing Oxfordshire score. Forty-one (14%) were lost to follow-up and two died before 3 months.	AliveCor KardiaMobile	12 lead ECG and Holter	1-Proportion of new AF detected using iECG recordings compared to Holter monitoring, in the subset of patients who received both investigations. 2-Proportion of patients with new AF detected using nurse-led iECG recordings. 3-Time from stroke onset to AF detection for

			Inclusion criteria: Patients were eligible for enrolment if they presented with ischemic stroke or TIA with no known AF, and no AF on the admission 12-lead ECG. **Exclusion criteria:** Patients were excluded if the treating medical team considered long-term oral anticoagulation use inappropriate because the stroke was very severe or in the light of other co-morbidities.			each monitoring method. 4-Proportion of patients anticoagulated at 3 months follow-up for each monitoring method and all methods combined for newly diagnosed AF.
Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study (Halcox et al., 2017)	**Author:** Halcox, J. P. J. **Year:** 2017 **Location:**	RCT	**Total population:** **5846 individuals** **Inclusion:** Individuals >65 years of age with a CHADS-VASc score ≥2 not in receipt of OAC therapy without a known diagnosis of AF currently, a known contraindication to anticoagulation or permanent cardiac pacing implantation were recruited.	AliveCor KardiaMobile	Routine clinical care (RC)	1-AF detection rate between the two arms 2-comparison of patients' compliance within the arms 3-patients satisfaction with device use

			Design: Of these, 3305 did not reply and 1269 declined participation. The 1272 volunteers were reviewed further by telephone/verbal screening; 240 did not meet criteria for inclusion (24 with AF not identified on initial notes review, 22 taking warfarin, 4 with a permanent pacemaker, 127 with no Internet access, and 63 miscellaneous) and were not invited for further screening. A further 28 1032 who attended for a screening visit were excluded, 18 because of a new AF diagnosis on screening iECG, and 10 for other reasons (including an inability to obtain interpretable iECG traces or to use the device properly [n=5], lack of access to the Internet [n=2],			

			or previously unidentified exclusion criteria [n=3]).			
High Burden of Unrecognized Atrial Fibrillation in Rural India: An Innovative Community-Based Cross-Sectional Screening Program(Soni et al., 2016)	**Author:** Soni A **Year:** 2016 **Location:** India	Observational/Cross-sectional	235 **Participants** Both AliveCor and pulse data were recorded serially for 2 minutes each on 5 consecutive days over 6 weeks beginning June 2015. During the screening, participants sat cross-legged, resting the smartphone (iPhone 4S) in their lap to stabilize the phone and reduce excess motion that could interfere with the recordings. **Excluded:** The AliveCor device malfunctioned for two weeks, and therefore 120 participants from two villages were not screened for atrial fibrillation using AliveCor and were excluded from this study.	**AliveCor KardiaMobile**	None	1-prevalence of AF in this region screened by AliveCor. 2-Overcoming resource limitation by using AliveCor device. 3-Serial screening of AF by AliveCor enhances the ability to identify persons at risk of AF.

Age-and-sex stratified prevalence of atrial fibrillation in rural Western India: Results of SMART-India, a population-based screening study(Soni et al., 2019)	**Author:** Soni A **Year**: 2019 **Location:** India	Observational/Population based screening study/Cross-sectional	**Total population:** 2100 Participants were screened using the Kardia Mobile device three times over five days. On the first screening day, the trained research coordinators administered a standardized questionnaire in the local language that was adapted to the cultural context using cognitive response testing. Exclude/withdraw: Of the 2100 participants enrolled in the SMART-India study, 26 were never screened for technical reasons; among those screened, 127 did not complete the study questionnaire	**AliveCor KardiaMobile**	None	1-The prevalence of AF screened by AliveCor device. 2-Enhancing the AF detection by increasing the screening period. 3-Prevalence of AF stratified by age and sex.

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Diagnostic Accuracy of a Smartphone-Based Atrial Fibrillation Detection Algorithm (Isma Nusrat Javed 2019)	**Author:** Isma Nusrat Javed et al. **Year:** 2019	Observational	**Total population:** 29 **patients** with AF and low CHADS2-VASc score **Duration of study**:20 months **Withdrawals:** 20 patients failed to submit a daily ECG at least once	Kardia mobile	Gold standard: Physician interpretation	1-number of the recorded ECGs 2-detection rate of the device 3-The sensitivity and specificity of the automated algorithm for the diagnosis of AF were compared against the physician interpretation as the gold standard.
Preliminary Results of Smartphone Electrocardiogram for Detecting Atrial Fibrillation After A Cerebral Ischemic Event: a Multi-center Randomised Controlled Trial (Koh et al., 2019)	**Author:** K.T. Koh, **Year:** 2019	RCT	Total population: 85 **participant** -one additional 24-Hour Holter monitoring **(control group)** -30-day smartphone electrocardiogram monitoring **(intervention group)** **inclusion criteria:** included age≥55 years old, without known AF, and	**Kardia** Mobile Cardiac Monitor (AlivCor®, Mountain View, CA)	24H **Holter** monitoring	1-the diagnostic yield of 30-day smartphone electrocardiogram recording compared to 24-hour Holter monitoring for detecting AF≥30 seconds.

			ischemic stroke or transient ischemic attack (TIA) within the preceeding12 months. **Exclusion**: Seven (8.2%) patients were excluded for various reasons. **Final population after exclusion:** The final preliminary analysis consisted of 40 patients in the control group and 38 patients in the intervention group.			
Evaluating smartphone-based photoplesy thomography as a screening solution for atrial fibrillation: A digital tool to detect afib? (Grieten et al., 2017)	**Author:** Grieten et al. Year: 2017	Observational /case-control	**Total population:** 1056 **patients** **The screening was performed using a:** • Single lead ECG device (AliveCor, 30 sec) measured between both hands • Camera-based photoplethysmography (FibriCheck, 60 sec) using the fingertip on the smartphone camera	**Fibricheck**	**AliveCor**	1-the quality performance of two device 2-the diagnostic capability of the two devices

Validation study of a pulse-deriving wrist band using spot-check measurements to detect atrial fibrillation (Dankers et al., 2019)	**Author**: Dankers et al. **Year**: 2019	Observational /cohort	Total population: 60 **subjects** **Inclusion criteria** older than 18 years and no cardiac device that could influence the heart rhythm	a wearable **PPG** wrist band (Wavelet health band, Wavelet)	**Kardia** band, AliveCor	1-Diagnostic performance of the two devices
Comparing a mobile ECG device with Holter monitoring for patients with palpitations in an urgent care setting: a preliminary study (Goel et al., 2018)	**Author:** Hersh V Goel, **Year**: 2018 **Location**: USA, Arizona	Observational /cross- sectional	Total Population: 50 **patients** **Design:** each patient was surveilled with a KM device for 1 month and concurrently with a Holter monitor for the first 24-hours of the study period. Patients were instructed to use the KM device when symptomatic.	**KM devise**	24H **Holter** monitoring	1-Comparison of diagnostic yield of two groups 2-Types of detected arrhythmia
iPhone Rhythm Strip: Clinical Implications of Wireless and Ubiquitous Heart Rate Monitoring(Saxon et al., 2012)	**Author:** Leslie Saxon **Year:** 2012 **Location**: India	Observational	Total population: 54 **participants** iPhone-owning attendees of a Body Computing Conference at USC participated in an 8-week study to determine how they utilize the device. ECG recordings were	**AliveCor KardiaMobile**	None	1-Physicians visits 2-The usability of device and ease of use by patients 3-Types of recorded traces

			reviewed daily by the principal investigator, a board-certified electrophysiologist.			
Smartphone Enabled ECG Recording Can Scale for the U.S. Heart Failure Ambulatory Population(Bose et al., 2014)	**Author:** Rupan Bose **Year:** 2014 **Location:** NR	Observational	**Number of users:** 8,669 persons Device users recorded real-time 30-second ECGs. - Tracings were wirelessly transmitted to a secure server (AliveCor, San Francisco, CA) - Data was analyzed and an FDA-approved algorithm was used to detect AF. - The study population included patients enrolled in clinical trials of the device (15% of patient population), as well as those who were prescribed the device and those who. purchased it over the counter for self-monitoring	**AliveCor KardiaMobile**	None	1-The compliance of patients for device use 2-Detection rate of AF
Detection of atrial fibrillation on ward rounds with AliveCor ECG in acute	**Author:** Philip, A. **Year:**	Observational	129 **Patients** All acute ischemic stroke patients were	**AliveCor KardiaMobile**	24-Holter monitoring	1-Detection rate of AF

ischemic stroke patient(Philip, 2016)	2016 **Location:** NR		enrolled in the study. The daily screening was done with AliveCor during morning and evening ward rounds. All patients also had standard cardiac rhythm evaluation during their hospital stay including 24-Holter monitoring. Patients noted to have AF on AliveCor were confirmed with a 12-lead ECG immediately.			2-Increased AF detection rate 3-Comparison of CHADS2 score of AF and non-AF patients
The role of symptoms in adherence to mHealth ECG monitoring for atrial fibrillation(Reading et al., 2017)	**Author:** Reading, M. **Year:** 2017 **Location:** NR	RCT	50 **adults** utilizing the AliveCor™ mHealth ECG monitor and application to determine differences in mHealth use and the association with symptoms over a 6-month follow-up period.	**AliveCor KardiaMobile**	None	1-Adherence rates and reasons for failing to transmit were captured.

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion), and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Atrial Fibrillation Health Literacy and Information Technology Trial in Rural PA Counties	**Completion date:** August 31, 2023 **Location:** USA, Pennsylvania **PI**: Jared W. Magnani	RCT	264 **participants** **Experimental:** -Intervention arm: Receive the relational agent and the AliveCor Kardia for use for 120 days. Participants are directed to use these interventions daily. -Active Comparator: Usual care arm Receive a brochure on atrial fibrillation that is published by the American Heart Association and a smartphone with the WebMD application. Participants are directed to use the WebMD application as often as they would like. **Inclusion Criteria:** 1. Adult, age ≥18. 2. Diagnosis of AF, identified from the EHR problem list and confirmed by 2 or more reports	Relational agent/**AliveCor Kardia –** Intervention Group: Use of the relational agent and Kardia daily for 120 days.	Use of the **WebMD app** daily for 120 days.	-Medication possession ratio -Self-reported adherence -Change from baseline Atrial Fibrillation Effect on QualiTy of life (AFEQT) -Emergency room visits -Urgent care visits -Days of hospitalization

			of AF from separate monitoring events at least 2 weeks apart (CG, Holter, or event monitor). 3. CHA2DS2-VASc (heart failure, hypertension, age, diabetes, prior stroke/TIA, CD, female sex) ≥2. 4. Prescribed use of warfarin or DOAC (formerly NOAC) for AF stroke prevention. 5. English-speaking well enough to participate in informed consent and this study. 6. No plans to relocate from the area within 12 months of enrollment. **Exclusion Criteria:** 1. Conditions other than AF require anticoagulation, such as a mechanical prosthetic valve, deep vein			

			thrombosis, or pulmonary embolism. 2. History of pulmonary vein isolation or foreseen pulmonary vein isolation. 3. History of AV nodal ablation or foreseen AV nodal ablation. 4. Heart failure necessitating hospital admission ≤3 months before study inclusion. 5. Acute coronary syndrome (defined as at least 2 of the following: chest pain, ischemic electrocardiographic changes, or troponin ≥0.1 ng/mL) ≤3 months prior to study inclusion. 6. Untreated hyperthyroidism or ≤3 months euthyroidism before inclusion.			

			7. Foreseen pacemaker, internal cardioverter defibrillator, or cardiac resynchronization therapy. 8. Cardiac surgery ≤3 months before inclusion. 9. Planned cardiac surgery. 10. Presence of non-cardiovascular conditions likely to be fatal within 12 months (e.g., cancer). 11. Inability to comprehend the study protocol, defined as failing to correctly answer a set of questions on orientation and short-term memory during the consent process.			
Atrial Fibrillation Health Literacy	**Completion date:** March 29, 2024	RCT	240 **participants**	**Experimental**: Intervention	**Active Comparator:**	-Medication possession ratio

and Information Technology Trial in Pittsburgh, PA (AFibLITT)	**Principal Investigator**: Jared W. Magnani **Location**: USA		**Inclusion Criteria:** 1. Adult, age ≥21. 2. Diagnosis of AF, identified from the EHR problem list and confirmed by 2 or more reports of AF from separate monitoring events at least 2 weeks apart (CG, Holter, or event monitor). 3. CHA2DS2-VASc (heart failure, hypertension, age, diabetes, prior stroke/TIA, CD, female sex) ≥2. 4. Prescribed use of warfarin or DOAC (formerly NOAC) for AF stroke prevention. 5. English-speaking well enough to participate in informed consent and this study. 6. No plans to relocate from the area within 12 months of enrollment.	arm: Receive the relational agent coupled with the **AliveCor Kardia** heart rate and rhythm monitor for 120-day use.	Usual care arm Receive a brochure on atrial fibrillation, the WebMD app, and the AliveCor Kardia heart rate and rhythm monitor for 120-day use.	-Self-reported adherence -Change from baseline Atrial Fibrillation Effect on QualiTy of life (AFEQT) -Emergency room visits -Urgent care visits -Days of hospitalization

			Exclusion Criteria: 1. Conditions other than AF that require anticoagulation, such as a mechanical prosthetic valve, deep vein thrombosis, or pulmonary embolism. 2. History of pulmonary vein isolation or foreseen pulmonary vein isolation. 3. History of AV nodal ablation or foreseen AV nodal ablation. 4. Heart failure necessitating hospital admission ≤3 months before study inclusion. 5. Acute coronary syndrome (defined as at least 2 of the following: chest pain, ischemic electrocardiographic changes, or troponin ≥0.1			

			ng/mL) ≤3 months prior to study inclusion. 6. Untreated hyperthyroidism or ≤3 months euthyroidism before inclusion. 7. Foreseen pacemaker, internal cardioverter defibrillator, or cardiac resynchronization therapy. 8. Cardiac surgery ≤3 months before inclusion. 9. Planned cardiac surgery. 10. Presence of non-cardiovascular conditions likely to be fatal within 12 months (e.g., cancer). 11. Inability to comprehend the study protocol, defined as failing to correctly answer a set of questions on orientation and short-term memory during			

			the consent process.			
Detecting atrial fibrillation, a common heart rhythm abnormality and preventable cause of devastating strokes, using smartphones in patients admitted to hospitals with strokes.	**Completion date:** None Registered on:2016. **Location:** Australia and china **PI**: Dr. Hans Tu	A non-randomized trial	**total sample** of 296 patients **Inclusion**: Patients with ischemic stroke or transient ischemic attack without known atrial fibrillation attending a participating stroke center with minimum age of18 Years. **Exclusion:** 1. Ischemic stroke or transient ischemic attack patients with known atrial fibrillation 2. Patients with isolated sensory change or vertigo without acute infarction on brain imaging	The **AliveCor** Mobile ECG device	**12-lead** electrocardiogram, cardiac telemetry and Holter monitoring	-Proportion of patients with new paroxysmal atrial fibrillation detected using AliveCor Mobile ECG compared to 12-lead ECG, Holter monitoring, and cardiac telemetry according to the current standard local paradigm. -Proportion of new paroxysmal atrial fibrillation detected using AliveCor Mobile ECG compared to Holter monitoring, in the subset of patients who received Holter monitoring. -Proportion of new paroxysmal atrial fibrillation detected using AliveCor mobile ECG compared to 12-lead ECG, in the subset of patients who

						received one or more 12-lead ECG during the admission. -Proportion of new paroxysmal atrial fibrillation detected using AliveCor mobile ECG compared to cardiac telemetry, in the subset of patients who received cardiac telemetry -Time from stroke onset to paroxysmal atrial fibrillation detection for AliveCor Mobile ECG, 12-lead ECG, Holter monitoring, and cardiac telemetry. -Proportion of patients who have been prescribed an oral anticoagulant daily (including Vitamin K antagonists, a direct thrombin inhibitor, and factor Xa inhibitor) by their treating stroke physician or family

						physician following AliveCor Mobile ECG monitoring compared to 12-lead ECG, 24 Holter monitoring, and Cardiac telemetry, as documented in the medical records at the participating stroke centers,
Early Diagnosis of Atrial Fibrillation in the Wait-Time Prior to Seeing a Cardiologist (CATCH-AF)	**Completion date:** July 2022 **Location:** Canada, British Columbia **PI**: Markus Sikkel	RCT	220 **participants** **Inclusion Criteria:** Age >18 Referral for episodic symptoms that may be due to arrhythmia (e.g., palpitations, dyspnea, or pre-syncope) At least one risk factor from CHADS-65 CCS Algorithm **Exclusion Criteria:** Previous diagnosis of atrial fibrillation Already anticoagulated for another diagnosis (e.g., metallic heart valve or pulmonary embolism) Symptoms typical of non-arrhythmic cause (e.g., exertional chest pain)	**Standard of Care** Holter monitoring	**Kardia**/AliveCor monitoring with additional Holter monitoring as needed	-Time to atrial fibrillation diagnosis compared between arms as analysed by Kaplan-Meier survival curves [Time Frame: 6 months] using the Log-rank test.

Evaluation of Ambulatory Monitoring of Patients After High-risk Acute Coronary Syndrome Using Two Different Systems: biomonitor-2 and Kardia Mobile	**Completion date:** December 1, 2021 **Location**: Spain **PI**: Felipe Rodríguez Entem	RCT	150 **participants** **Inclusion Criteria:** The patient can understand the nature of the study and has provided written informed consent. Patient with Acute Coronary Syndrome, with or without elevation of the ST segment at the EKG (the last with an elevation of troponins). Patient with coronagraphy at the episode of ACS showing severe lesions treated with a stent. Patient with risk index for 6-month mortality (GRACE score) of more than 118. Patient with risk index for stroke (CHA2DS2-VACS score) of more than 2. **Exclusion Criteria:** Patient with history of AF. Patient with episodes of AF during admission at the current episode.	Biomonitor-2 and **Kardia** mobile	**Standard care/not mentioned clearly**	-Detection rates for atrial fibrillation (AF / atrial flutter) during the follow-up. -Detection rates of ventricular arrhythmia in the electrocardiogram (EKG) during the follow-up. -Detection rates of advanced conduction abnormalities and significant ST shifts (> 1 mm) in the EKG. -Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) -Number of Re-hospitalizations during the follow-up. -Correlation of primary outcomes between Biomonitor-2 versus Kardia Mobile

			Patient with a pacemaker or ICD (implantable cardioverter-defibrillator) previously. Patient with an indication of pacemaker or ICD in current or short-term phase. The patient is participating in another interventional clinical investigation. The patient is pregnant or breastfeeding. The patient´s life expectancy is less than 24 months.			
A Fib Clinic of the Future Using KardiaPro Platform for Chronic Care of Patients With AF After Ablation Procedure	**Completion date:** December 2021 **Location:** United States, Ohio **PI**: Khaldoun G Tarajki	RCT	**100 participants** **Inclusion Criteria:** 1. 18-85 years old 2. Have a smartphone with a data plan. 3. History of AF (paroxysmal or persistent) 4. In sinus rhythm at the 3–4-month post-procedure visit and no evidence of AF during the interval	**Kardia** Monitoring	**Standard** of Care Monitoring	-Time to atrial fibrillation detection -Incidence of atrial fibrillation after successful AF ablation -Average number of atrial fibrillation episodes detected after successful ablation -Average number of clinical encounters after successful ablation

			starting after the 3-week blanking period and ending at the appointment time. 5. On Anticoagulation if CHADS VASC score is ≥ 1 and will continue to be on anticoagulation or CHADS VASC of Zero 6. Willing to follow up with their Cleveland Clinic electrophysiologist in 6 months. **Exclusion Criteria:** 1. Patients without smartphone 2. Unwilling to provide consent. 3. Unwilling to follow up in 6 months. 4. CHADS VASC ≥ 1 and anticoagulation will be stopped. 5. Presence of a cardiac implantable electronic device			-Use of alternative monitoring devices after successful ablation -Change in level of anxiety from the date of AF ablation to the end of the study period

			6. If the primary electrophysiologist decides the patient still needs monitoring through traditional monitors due to any reason			
Smart phone-based single lead ECG versus traditional ambulatory Holter monitoring to aid diagnosis of cardiac arrhythmias in patients with rapid heart rhythms	**Completion date:** Not available	RCT	**INCLUSION CRITERIA**: 1. Patients aged greater than or equal to 18 years. 2. Symptomatic palpitations in whom the initial 12 lead ECG has failed to detect arrhythmia. 3. At least two episodes of palpitations in the preceding 6 months. 4. Have a smartphone and/or a smartwatch capable of running the AliveCor application.	**AliveCor** KARDIAMOBILE	**Holter** monitor recording	-compliance with sECG device -diagnosis of an arrhythmia by device
Metformin as an Adjunctive Therapy to Catheter Ablation in Atrial Fibrillation	**Completion date:** November 2022 **Location**: United States, Michigan	RCT	150 **participants** **Inclusion Criteria:** Body Mass Index (BMI) >25 kilograms / square meter (kg/m2) with a plan for rhythm control of atrial	**AliveCor**	**none**	-Burden of Atrial Fibrillation assessed by AliveCor Kardia Devices -Freedom from recurrent atrial arrhythmias by 6

	PI: Hakan Oral		fibrillation by catheter ablation All subjects must be able to understand and willing to sign a written informed consent document. **Exclusion Criteria:** Individuals who are already taking metformin or other antidiabetic medications, including insulin Known diabetes. Known allergy or Food and Drug Administration (FDA)-labeled contraindication to taking metformin (estimated glomerular filtration rate (eGFR)<30 milliliters per minute (mL/min)/1.73 square meters (m2), hypersensitivity to metformin, acute or chronic metabolic acidosis) Patients taking carbonic anhydrase inhibitors. eGFR below 30 mL/min per 1.73 m2 or other clinical diagnoses of advanced renal disease Acute or chronic metabolic acidosis			months after a single ablation to eliminate AF -Time to recurrence of atrial fibrillation after a 3-month blanking period of ablation -Freedom from recurrent atrial arrhythmias at 1 year after ablation after the blanking period of 3 months -Freedom from recurrent atrial arrhythmias at 6 months after repeat ablation -Atrial Fibrillation Severity Score (AFSS) -Percent change in weight at 3 months after ablation -Percent change in weight at 6 months after ablation

			(serum bicarbonate <22 milliequivalents per liter (mEq/L)) History of significant alcohol use (>2 drinks/day on average) History of hepatic dysfunction (serum bilirubin 1.5 times greater than ULN) History of New York Heart Association (NYHA) Class III or IV heart failure Pregnancy or nursing			-Percent change in hemoglobin A1c at 6 months after ablation -Percent change in hemoglobin A1C at 12 months after ablation -Incidence of major procedural complications -Atrial Fibrillation related morbidity during follow-up
Pulsewatch: Smartwatch Monitoring for Atrial Fibrillation After Stroke	**Completion date:** December 31, 2021 **Location**: United States, Massachusetts **PI**: Timothy Fitzgibbons	RCT	120 **participants** **Inclusion Criteria:** History of Transient Ischemic Attack (TIA) or stroke or at risk for stroke based on a CHA2DS2-VASc score equal to or greater to a score of 3, presenting at the UMass Memorial Medical Center (UMMMC) inpatient service or ambulatory clinic (neurology clinics and cardiovascular clinics included) Age: greater to or equal to 50 years of age	**Pulsewatch system**	**Kardia** Mobile by AliveCor	-Usability of Pulsewatch System: System usability scale & Rating Scale -Detection of Atrial Fibrillation

			Able to sign an informed consent. Willing to participate in a focus group and/or Hack-a-thon for Aim 1 participants only. Willing and capable of using Pulsewatch (smartwatch and smartphone app) daily for up to 44-days and returning to UMMMC for up to two study visits for Aims 2 and 3 participants only. **Exclusion Criteria:** Major contraindication to anti-coagulation treatment Plans to move out of the area over the 44-day follow up period. Serious physical illness (e.g., unable to interact with a smart device, or communicate verbally or via written text) that would interfere with study participation. Known allergies or hypersensitivities to medical-grade hydrocolloid adhesives or hydrogel.			

			Patients with life-threatening arrhythmia's require in-patient monitoring for immediate analysis. Patient with an implantable pacemaker as paced beats interfere with ECG readings. Lacking the capacity to sign the informed consent. Unable to read and write in English. Plans to move from the area during the study period. Unwilling to complete all study procedures. Major contraindication to anti-coagulation treatment (i.e., major hemorrhagic stroke) Individuals who are not yet adults Pregnant women Prisoners			
Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics	**Completion date:** October 2021 **Location:**	RCT	35,308 **participants** **Inclusion Criteria:** Patients aged 65 years or older.	**AliveCor** KardiaMobile EKG Monitor	**none**	-Incident AF during the study period -Incident AF associated with a primary care

	United States, Massachusetts **PI**: Steven Lubitz		Presenting for an outpatient clinic appointment at a participating clinic Visit with a physician, nurse practitioner, or physician's assistant. **Exclusion Criteria:** Have a primary care physician outside of the network. Do not visit their primary care practice during the study period.			encounter during the study period -New oral anticoagulation prescription during the study period -New ischemic stroke within 24-months of the study start -Major hemorrhage within 24-months of the study start
Individualized Studies of Triggers of Paroxysmal Atrial Fibrillation	**Completion date:** February 2021 Not published but completed trial/no result available. **Location**: United States, California **PI**: Gregory M Marcus	Open labeled RCT	500 **participants** **Inclusion Criteria:** symptomatic paroxysmal AF a smartphone **Exclusion Criteria:** Non-English speakers Children (age < 18 years) Patients with plans to substantially change AF management (such as with ablation or change in antiarrhythmic drugs) over the ensuing 6 months.	**Participants in the N-of-1 arm** will use the Eureka mobile application and **AliveCor** device to tracking their AF episode frequency and severity and execute at least one N-of-1 trial to identify and better control their AF triggers.	**Participants in the data tracking arm** will use the Eureka app and **AliveCor** device to record daily AF frequency and severity and daily AliveCor readings for 10 weeks.	- Atrial fibrillation quality of life

			Unwillingness to test AF triggers. Patients who have had an AV node or AV Junction ablation			
Smartphone Electrocardiogram for Recording Atrial Fibrillation After a Cerebral Ischemic Event (SMART-AF)	**Completion date:** July 30, 2021 **Location**: Malaysia **Principal Investigator**: Keng Tat Koh	Open-label RCT	233 **patients** **Inclusion Criteria:** i. Age 55 years or older. ii. Diagnosis of the index event made by a neurologist or general physician of an acute ischemic stroke or TIA (WHO definition) of undetermined etiology occurring within the previous 6 months (180 days). The event must be either: An ischemic stroke confirmed by neuroimaging; or A transient ischemic attack, defined as involving a focal unilateral motor deficit, speech/language deficit, or hemianopia, with symptom duration <24 hours (note: amaurosis fugax/ transient monocular blindness, pure sensory spells, isolated vertigo spells,	Smartphone ECG, **AliveCor**	24 Hour **Holter** monitoring	-Detection of one or more episodes of atrial fibrillation or atrial flutter ≥30 seconds as assessed at the 30-day follow-up. -Proportion of patients prescribed with oral anticoagulation, a assess at the 30-day follow-up

			etc. do not qualify for enrolment given the potential for misdiagnosis of such events). iii. Patient meets the following: 1. At least one 12-lead ECG has already been obtained as part of the routine clinical post-stroke/TIA workup and not ECGs have shown any episodes of AF or atrial flutter. 2. A Holter monitor has already been obtained as part of the routine clinical post-stroke/TIA work-up and does not show any episodes of AF or atrial flutter ≥30seconds. iv. The patient is being actively investigated for the etiology of the stroke/TIA event and an additional cardiac monitor is desired to screen further for the			

			possibility of AF or atrial flutter. v. The following diagnostic test have already been completed as part of clinical routine post-stroke/TIA: 1. Brain imaging with CT or MRI 2. Vascular imaging of the extracranial and intracranial circulation with either CT angiography or MRI angiography to exclude significant large vessel occlusion disease as the most likely mechanism for index ischemic event (carotid Doppler ultrasound is acceptable for those presenting with anterior circulation ischemic events). * 3. Transthoracic (or transesophageal) echocardiography to exclude thrombus or			

			another structural heart disease that in the opinion of the investigator is the most likely cause for the stroke/TIA events. * *(if a baseline investigation cannot be obtained clinically after the index event and before study enrolment, then it is acceptable for study purposes for investigations to be obtained after patient enrolment into the study but prior to the 90-day follow-up visit.) vi. Informed consent from the patient (or from a legally authorized representative if the patient is not competent, due to stroke-related cognitive impairment, aphasia, or anosognosia).			

			vii. The patient is expected to survive at least 12 months. **Exclusion Criteria:** i. Any previously documented atrial fibrillation or atrial flutter (a remote history of transient AF during the perioperative period is not exclusionary). ii. Exclusively retinal stroke or retinal TIA event. iii. A most responsible etiological diagnosis for the qualifying stroke/TIA event has already been determined i.e., cervicocephalic artery dissection, venous sinus thrombosis, hypercoagulable states, or other known cause. iv. Planned carotid endarterectomy within 90 days. v. Any finding on echocardiography for which there is already an evidence-based indication for long-term anticoagulation (e.g., mechanical heart valve, thrombus, etc.) vi.			

			Inability to use the AliveCor smartphone ECG monitor upon enrolment into the study (if the patient is randomized into an interventional group). * vii. Participating in a clinical trial involving investigational medication. viii. Endocarditis. ix. Pregnancy.			
Health eHeart BEAT-AFib - Health eHeart Biomarkers of Early Atrial Transformation in Atrial Fibrillation (BEAT-AFib)	**Completion Date:** September 15, 2040 **Location**: USA **PI**: Jeffrey E Olgin	Observational cohort	3000 **participants** **Inclusion Criteria:** 1. At least 18 years of age or older 2. English speaking 3. Able to consent. 4. ANY one of the following criteria: A history of non-valvular AF or AFL documented on ECG or ambulatory monitoring within 1 year of enrollment. Two or more of the following criteria if no history of AF: Age > 65 years of age	**AliveCor**	**None**	-detection of arrhythmias by use of ambulatory ECG monitoring -Progression of AF -Recurrence of AF after treatment with direct current cardioversion (DCCV) or AF ablation -Symptom Burden [AF Group]

			A diagnosis of hypertension A diagnosis of diabetes A diagnosis of sleep apnea A BMI ≥ 30 Stable HF with preserved or reduced ejection fraction (NYHA Class I, II, or III) CKD not requiring dialysis. More than 5% PAC burden on ambulatory ECG monitoring (e.g., Holter, Ziopatch, Lifewatch, etc.) Patients undergoing EP study or ablation for SVT with no history of AF and not meeting any of the above criteria (a-c). **Exclusion Criteria:** 1. Life expectancy < 1 year 2. Reversible causes of AF (e.g., postoperative AF, cardiac surgery, pulmonary embolism,			

			untreated hyperthyroidism) 3. Pregnant at the time of enrollment 4. Unwilling/unable to perform follow-up using digital follow-up. 5. CKD requiring dialysis. 6. Presence of a condition or abnormality that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data. 7. Patients undergoing active cancer treatment or diagnosed with cancer requiring treatment in the last 2 years.			
Validation of a Novel Smartphone-based Method for Heart Rhythm	**Completion Date:** December 2021 **Location**:	Observational cohort	480 **Participants** **Validation cohort:** **Inclusion Criteria:**	**AliveCor** Kardia Mobile ECG and Smartphone camera PPG recordings	**None**	-Performance of the novel smartphone-based photoplethysmographic method for heart rhythm diagnostics

Monitoring in the Home Environment	Sweden **PI**: Johan Engdahl		Patients undergoing direct current cardioversion successfully for the treatment of atrial fibrillation or atrial flutter and have a normal heart rhythm after the treatment. **Exclusion Criteria:** Patients with implantable cardiac devices. **Clinical implementation cohort:** **Inclusion Criteria:** Patients planned for direct current cardioversion for treatment of atrial fibrillation or atrial flutter. **Exclusion Criteria:** Patients with implantable cardiac devices. Patients with a spontaneous return to sinus rhythm diagnosed at a screening visit 2 to 4 weeks before the scheduled treatment with direct current cardioversion.	using a novel software application.		and discrimination of atrial fibrillation from normal heart rhythm -Independent predictors for recurrence of atrial fibrillation within 30 days of treatment with direct current cardioversion -Participant compliance for recording heart rhythm with the novel smartphone-based method twice daily for 30 days

Home-Based ECG- detection of Arrhythmia with Ambulatory Recorded ECG	**PI:** Senthil kirubakaran **Year:** 2021 **Location**: UK	Observational	**200 Participants** **Inclusion criteria:** 1. Patients referred to Cardiology Outpatient department with symptoms of palpitations, pre-syncope, syncope consistent with arrhythmia, and continuous duration of symptoms > 1min. 2. Symptom frequency is less frequent than weekly. 3. Aged 18 and above. 4. Able to provide informed consent. 5. Able to use ambulatory ECG device +/- AliveCor app. **Exclusion criteria:** 1. Asymptomatic patients are referred to the Cardiology Outpatient Department for a screening of possible arrhythmia including patients who are investigated following TIA/stroke. 2. Patients referred to Cardiology Outpatient department with	Each eligible patient will be provided with a **KardiaMobile** for 3 months or until symptom-rhythm correlation occurs.	**None**	-Proportion of patients with-established symptom-rhythm correlation -Proportion of patients in whom significant cardiac arrhythmias were detected -Proportion of patients in whom atrial fibrillation was detected -Proportion of patients subsequently assessed for starting anti-coagulation. The proportion of patients who had other types of cardiac arrhythmia detected which required further treatment

			symptoms of palpitations, pre-syncope, syncope consistent and red flag symptoms or duration of symptoms < 1min. 3. Symptom frequency more than weekly. 4. Patients on anticoagulation and/or with an established diagnosis of cardiac arrhythmia (atrial/ventricular arrhythmia). Patients are unable to use the device +/- app.			

Table 4 Results of all relevant studies (from tables 1, 2, and 3)

Study	Results	Company comments
Recurrent atrial fibrillation/ flutter detection after ablation or cardioversion using the AliveCor KardiaMobile device: iHEART results (Goldenthal et al., 2019)	- **Procedure at enrolment:** Intervention group: DCCV n=55 (48%) RFA n=80 (52%) Control group: DCCV n=60 (65%) RFA n=43 (35%) - **Documented recurrence AF/AFL:** 1-Control group: 49 (41.5%) 2-Intervention group: 58 (50.4%) 3-The likelihood of recurrence detection was significantly greater in the intervention group (hazard ratio = 1.56, 95% CI: 1.06-2.30, P = .024). - **Rate of Treatments of recurrence:**	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat

	4-In control group: 35 (71.4%) 5-Intervention group: 21 (36.2%) 6-Patients with recurrent AF/AFL in the intervention group were less likely to be treated than those in the control group (hazard ratio = 0.33, 95% CI: 0.57-2.92, P < .0001). Regardless of whether patients underwent DCCV or RFA, recurrence was detected earlier in the intervention group. 7-All-cause hospitalizations and emergency room visits did not differ significantly between arms. - When AF patients are compliant with daily use of home ECG monitoring, recurrent arrhythmias are discovered earlier when compared to control patients. - The AliveCor KardiaMobile home monitoring device is mostly beneficial for prompt detection of early (first month) recurrence after RFA or DCCV, and that early recurrence predicts late recurrence.	hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Avoiding unnecessary referral to secondary care.
Evaluating the Utility of Mhealth ECG Heart Monitoring for the Detection and Management of Atrial Fibrillation in Clinical Practice (Hickey et al., 2017)	- **AF/AFL detected:** 1-Intervention group: n=14 (61%) 2-Control group: n=7 (30%) 3-Hazard ratio= 2.55 95% CI= 1.06 to 6.11, p = 0.04 - **4-Quality-of-life assessments:** - At baseline and 6 months: Intervention group: n=13 PCS scores increased significantly from 50.3 +/- 7.6 to 55.9 +/- 5.3 (p = 0.02).	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	- Significant increases were observed for: (mean + SD) Physical functioning scores 49.9 + 7.7 to 55.7 + 2.5, Role physical scores 44.0 + 11.4 to 55.5 + 4.8, Vitality scores 45.3 + 11.2 to 54.3 + 8.1 Mental health domain scores 42.6 + 7.2 to 50.9 + 8.5. Mental component summary scores did not change significantly from baseline to 6 months (47.5 +/- 7.2 and 51.7 +/- 9.6, respectively). **Survey**: - 5-At 6 months, none of the patients in the ECG monitoring group reported trouble using the device. - Additionally, there was no difference in the rate of hospitalizations between the ECG monitoring group and the control group; no deaths occurred during follow-up.	
Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone electrocardiogram (Lowres et al., 2016)	**Male**: 35 (80%) **The mean age**: 69 ± 9 years **1-Detected AF recurrence:** in 10/42 participants **2-Tracing records:** During the study, 3481 iECGs were recorded, of which 146 (4%) were non-diagnostic because of hand tremors, or poor mobile reception. **3-Accuracy of detection: (sensitivity)**	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure

	The algorithm had high accuracy for detection of AF, with a sensitivity of 94.6% (95% CI, 85.1–98.9) and specificity of 92.9% (95% CI, 92.0– 93.8) **4-Survey: Usability** The iECG was reported to be easy to use by 95% of participants and surprisingly age was not a barrier (age range 45–85 years. Only 2 participants reported they needed a 'familiarization period'. 5- **False positive reasons:** The majority of false-positive iECGs were associated with low-voltage p-waves and QRS complexes, atrial ectopy, and left bundle branch block. Interestingly, 81% of participants were also identified with atrial and/or ventricular ectopy, or sinus arrhythmia during the study period. iECGs were recorded for a mean of 29 ± 5 days (range 9– 46), with 86% of participants recording iECGs for 27 days or more, and only 2 participants (5%) recording for <21 days. A mean of 2.8 ± 0.9 iECGs was recorded per day. 6-Within 3 weeks of discharge (range 1–17 days), self-monitoring with the iECG detected a POAF recurrence in 10/42 participants, equating to 24% (95% CI, 12–39%) 7-These participants (mean age 64 ± 7 years) were on average 7 years younger than those without AF recurrence (mean age 70 ± 10 years) P = 0.025. No association was noted for gender nor comorbidities including body mass index (BMI).	

	Results for the AF knowledge questionnaire (total score out of 10) improved from a mean of 6.4 ± 1.8 to 7.3 ± 1.8 (P = 0.02).	
A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs (Selder et al., 2019)	A total of 233 participants in Hartwacht were included in the study. **Tracing records:** **1-Number of ECGs:** During the study period, 5,982 KM ECGs were received, with a median of 28 ECGs per patient per year. Of these. **2&3**-The KM algorithm categorised 3,548 (59%) as normal sinus rhythm, 1,301 (22%) as possible atrial fibrillation, 1,033 (17%) as unclassified and 100 (2%) as unreadable. Classification of the ECGs by the KM algorithm and diagnosis of the Hartwacht team (Cardiologist) differed significantly. **4**-When the ECG was classified as sinus rhythm by the KM algorithm, the Hartwacht team agreed in 96%. normal sinus rhythm by KM= 3,548 sinus rhythm by cardiologist= 3,394 (96%) When possible, AF was detected by the KM algorithm, the Hartwacht assessment confirmed AF in 80% of cases. Possible atrial fibrillation by KM= 1,301 atrial fibrillation by cardiologist= 1,042 (80%)	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.

	5-Device performance/Sensitivity: Using the assessment of the Hartwacht team as reference standard, for diagnosing AF Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) was 0.92, 0.95, 0.80, 0.98 and 0.94 respectively (upper table); for normal sinus rhythm (without any PACs or PVCs) 0.85, 0.83, 0.90, 0.76 and 0.84, (middle table); and for any form of sinus rhythm (with or without PACs or PVCs) 0.80, 0.91, 0.96, 0.65 and 0.83, respectively. - The KM device provides a patient-initiated 30-second one-lead ECG of diagnostic quality in ambulatory arrhythmia patients. - Less than 10% of the ECGs were uninterpretable. For detection of AF, the KM algorithm provides a high NPV, but PPVis relatively low, resulting in the need for manual assessment of all ECGs categorized as other than normal sinus rhythm.	
The IPED (Investigation of Palpitations in the ED) Study: Multi-center Randomized Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED (Investigation of Palpitations in the ED) study (Reed et al., 2019)	1-**A symptomatic rhythm**: was detected at 90 days in 69 (n = 124. 55.6%; 95% CI 46.9–64.4%) participants in the intervention group versus 11 (n=116; 9.5%; 95% CI 4.2–14.8) in the control group (RR 5.9, 95% CI 3.3–10.5; p b 0.0001). **2-A symptomatic cardiac arrhythmia:** Detected at 90 days in 11 (n = 124; 8.9%; 95% CI 3.9–13.9%) participants in the intervention group versus 1 (n=116; 0.9%; 95%CI 0.0–2.5%) in the control group (RR 10.3, 95% CI 1.3–78.5; p = 0.006). **3-The mean time to symptomatic rhythm detection**:	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	In the intervention group was 9.5 days (SD 16.1, range 0–83) versus 42.9 days (SD 16.0, range 12–66) in the standard care group (p b 0.0001). **4-The mean time to symptomatic cardiac arrhythmia detection**: In the intervention group was 9.9 days (SD 15.6, range 1–55) versus 48.0 days (1 participant) in the control group (p= 0.0004) **5-Symptomatic cardiac arrhythmias were**: AF (8 intervention, 0 standard care), SVT (3 intervention, 0 standard care), sinus bradycardia (0 intervention, 1 standard care) and atrial flutter (1 intervention, 0 standard care). **6-Serious outcome:** At 90 days in the intervention group was 11 (8.9%) versus 2 (1.7%) in the control group (p = 0.02) **7-Undergoing treatment:** At 90 days, 12 participants in the intervention group were subsequently undergoing (or planning to undergo) treatment for symptomatic cardiac arrhythmia versus 6 in the control group (p = 0.192). **Survey:** Eighty of 92 (87.0%) participants found the AliveCor monitor easy to use. **8-ED (Emergency Department) Presentations:** -There were more ED presentations (after index visit) due to palpitations/pre-syncope in the intervention group (12/124; 9.7%; 95% CI 4.5–14.9% with 1 or more	• Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.

	non index ED presentations) compared to the control group (3/116; 2.6%; 95% CI 0.0–5.5%; p = 0.031). -There was no difference in the number of participants with one or more inpatient hospital days (over all admissions) due to palpitations or pre-syncope in the intervention group (2; n = 122; 2 patients with no data; 1.6%; 95% CI 0.0–3.8%) compared to the control group (1; n =116; 0.9%; 95% CI 0.0–2.5%; p N 0.999), number of outpatient presentations due to palpitations or pre-syncope (p = 0.058), number of GP presentations due to palpitations or pre-syncope (p = 0.312) or number of ECGs performed due to palpitations or pre-syncope (p = 0.143). The use of a smartphone-based event recorder increases the symptom–Rhythm correlation rate over five-fold at 90 days with a reduced cost per diagnosis. -In patients presenting with palpitations or near syncope the incorporation of a patient activated detection device into routine practice may overcome some of the current difficulties in diagnosis caused by the normalization of a smartphone-based event recorder could improve clinical care and patient experience for those suffering undiagnosed palpitations and pre-syncope cardiac rhythm by the time the patient undergoes a clinical assessment. -More patients had a subsequent ED attendance in the intervention group compared to the control group. -The patients found the monitor easy to use. -This study suggests that the AliveCor technology performs effectively and safely.	

Modified positioning of a smartphone-based single-lead electrocardiogram device improves detection of atrial flutter(Rajakariar et al., 2018)	**1-A total of 61 AKM tracings was obtained:** **2**-Including lead-I AFL (n = 11), lead II AFL (n = 11), lead-I AF (n = 14), and lead-I SR (n = 25). Overall, 18% of all tracings were in the setting of tachycardia (heart rate ≥100 bpm), 4.9% in bradycardia (heart rate b50 bpm), and the remaining ECGs in the normal HR range. -AKM tracings of sinus rhythm revealed no atrioventricular block or sinus arrhythmia, with rare atrial and ventricular premature beats. **3-Sensitivity of EPs:** -Compared to the 12 lead ECG as the reference standard, Eps (two electrophysiologists) demonstrated 100% sensitivity for detection of AF with no false-negative diagnoses. Mean sensitivity was 98% in SR (EP1 96%, EP2 100%) with one false negative. In comparison, the automated AKM diagnosis revealed 100% sensitivity in AF and 88% in SR (Sinus Rhythm). **4-Clinician detection of AFL**: Was poor using standard lead-I placement, with both EPs demonstrating a sensitivity of27%. Among misdiagnosed AFL lead-I cases, 37% of patients were identified as SR, all of which were AFL with fixed atrioventricular block. -Overall clinician agreement (AF, SR, and AFL) demonstrated modest agreement when utilizing lead-I (EP1: κ =0.71, EP2: κ = 0.73, p b 0.001). **5-Sensitivity of modified position:** Using the modified lead-II positioning for detection of AFL, sensitivity increased to 72.7% and 54.6% for EP1 and EP2 respectively.	• Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.

	-Significant improvement of overall clinician agreement (AF, SR, and AFL) was observed with the utilization of lead-II tracings (EP1: κ=0.87, EP2: κ=0.83, both p b 0.001) **6**-AKM automated diagnosis of AFL in lead-I demonstrated that 36.4% were diagnosed as AF, 45.5% as SR, and 18.2% unclassified. In contrast, lead-II AKM tracings of AFL were labeled AF in 9.1%, SR in 36.4%, and unclassified in 54.5%. Direct comparison between AKM and clinician diagnosis of AFL was not undertaken due to the device not proffering AFL as a diagnosis. -EPs demonstrated poor sensitivity for detection of AFL with standard lead-I ECG. -Repositioning of the AKM device to create a lead-II trace resulted in a marked improvement in clinician diagnosis of AFL.	
Validation of a smartphone-based event recorder for arrhythmia detection(Narasimha et al., 2018)	**1&2-Tracing records and types:** -The KM device had a total of 1,230 recorded tracings (roughly 30–35 tracings/patient). -Of these, 563 were sinus rhythm and 667 tracings had findings, such as sinus tachycardia, sinus bradycardia, sinus arrhythmia, premature atrial contractions (PACs), premature ventricular contractions (PVCs), atrial fibrillation, atrial flutter, and supraventricular tachycardia (SVT). -Of the 563 normal sinus rhythm tracings recorded by the KM device, 335 were recorded by patients as part of the protocol requiring twice-daily recordings with the KM device and were not associated with symptoms. The remaining 895 tracings (72.8%), consisting of both	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.

	sinus rhythm and other rhythms, were patient-initiated recordings because of symptoms. **Overlapping records:** -There was a total of 789 overlapping prescribed monitoring days using both devices. Of these 789 days, the KM device had 266 days (33.7%) in which a diagnostic recording of asymptomatic arrhythmia was made, compared to 161 days (20.4%) in which a diagnostic recording was made with the ELR. **3-Device compliance:** -The fact that the KM device recorded more symptomatic arrhythmias than the ELR indicates that, while the KM device was used as recommended by a majority of patients, compliance with ELR use was poor. **4-Compliance comparison of KM Vs. ELR:** -Overall compliance (percentage of days that the patient had at least one recording during the monitoring period) was significantly greater for the KM (91.2%) than for the ELR (52.7%, P < 0.01). **5-Detection rate:** -Analysis showed a failure to reject the null hypothesis that there was a difference in the detection rate of symptomatic arrhythmias between the devices (P > 0.05). -Analysis showed the percentage of days with at least one diagnostic recording was significantly higher with the KM device than with the ELR (χ2 = 61.9, P < 0.001). -The KM device recorded an arrhythmia on 276 (34.9%) of the 789 monitoring days, whereas the ELR	• Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.

	had 295 days (37.4%), which were statistically equivalent (P < 0.01) during the TOST procedure. -More patients had a potential diagnosis for their symptoms (i.e., at least one recorded symptomatic arrhythmia during the entire monitoring period) with the KM than with the ELR (KM = 34 [89.5%] vs ELR = 26 [68.4%)]; $\chi 2$ = 5.1, P= 0.024). **Types of detection:** -The most common symptomatic arrhythmias detected by the KM were: PACs (45.5%), sinus tachycardia (42.2%), and PVCs (33.3%). -The most common symptomatic arrhythmias detected by the ELR were sinus tachycardia (36.4%), PVCs (33.3%), and sinus bradycardia (24.2%). -The KM device was potentially diagnostic in 11 more patients for PACs than the ELR (P < 0.01). **6-Device yield:** -For both overall and specific arrhythmias, the KM yield of symptomatic recordings was greater than that of asymptomatic recordings. However, the ELR yields for symptomatic and asymptomatic recordings were not significantly different from one another. -In the ITT sample, the percentage of patients with any detected arrhythmias using the KM (92.1%) versus the ELR (84.2%) was statistically similar ($\chi 2$ = 1.1, P = 0.287). Similarly, the percentage of any detected arrhythmias using the KM (100%) versus the ELR (90.9%) in the PP sample was not statistically different ($\chi 2$ = 3.1, P = 0.076).	

	-A smartphone ECG recorder (KM) is non-inferior to an external ELR for the evaluation of palpitations. -Although ELRs provide extended periods of rhythm monitoring and real-time data, a significant percentage of patients are non-compliant with the requirement that these devices be worn continuously. -The patient yield for asymptomatic arrhythmias was significantly higher for the ELR than for the KM device. -KM device provides accurate, reliable real-time data to both users and healthcare providers that can be accessed easily and rapidly. -The KM is an attractive option for the initial diagnosis of palpitations in stable, relatively low-risk patients.	
Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: The iTransmit study(Tarakji et al., 2015)	**1&2-Tracing records: types** There were 831 AHM recordings. -Of these, 389 were simultaneous recordings with the TTM, and 442 were AHM recordings only. -Of the 831 AHM recordings, 7 were noninterpretable. Of the 389 simultaneous recordings, 4 AHM and 1 TTM recordings were noninterpretable. The κ statistic to assess agreement between AHM and TTM recordings was 0.82, indicating excellent agreement. **3-Detection rate:** -The AHM was able to detect sinus rhythm 97% of the time and correctly detected AF and atrial flutter 100% of the time, with 3% false-positive results. **4-Sensitivity:** If AF and atrial flutter are considered as one diseased state, the AHM had 97% specificity and 100% sensitivity.	Supports aimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	Survey: Of the 55 surveys completed, 40 (73%) showed that AHM recordings were as good as TTM recordings, 8 (14%) showed that AHM recordings were worse than TTM recordings, and 7 (13%) showed that AHM recordings were better than TTM recordings. **5-Device compliance:** More patients found the AHM easy to use compared to the TTM and felt that they had better access to the AHM whenever they had symptoms. -The AHM is an alternative method for monitoring patients after the AF ablation procedure, with 100% sensitivity and 97% sensitivity in the detection of AF and atrial flutter. -In general, patients' feedback on the ease of use of this technology is positive.	
Wireless Smartphone ECG Enables Large-Scale Screening in Diverse Populations (Haberman et al., 2015)	**Sensitivity:** **1-Sensitivity and Specificity of Smartphone ECG for Atrial Fibrillation/Flutter:** -**Athletes** N=123 (sensitivity NA/ Specificity =99.2%) -**HYA** N=128 ((sensitivity NA/ Specificity =100%) -**Patients** N=130 ((sensitivity 94.4%/ Specificity =99.1%) -**Total** N=381 (sensitivity 94.4%/ Specificity =99.4%) **2-Device compliance:** The vast majority of subjects found the wireless ECG more convenient and comfortable. -Smartphone (lead I) ECG tracings are easier and more efficient to obtain than those from a traditional 12-lead.	Supports aimed at benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.

	-The device yields accurate baseline conduction intervals and can detect atrial rhythm abnormalities with a high degree of sensitivity and specificity. -Wireless smartphone-enabled ECGs can be used for large-scale screening for detection of rate, conduction intervals, and common arrhythmias such as AF	
Assessing the accuracy of an automated atrial fibrillation detection algorithm using smartphone technology: The iREAD Study (William et al., 2018)	**1-Tracing records:** There were 225 simultaneous 12-lead ECG and KMCM recordings. -Of these, 62 recordings (27.6%) were “unclassified” by the KMCM algorithm and 2 ECGs were non-interpretable by the interpreting physicians. **2-Device Sensitivity:** Of the remaining 161 interpretable simultaneous recordings, KMCM automated algorithm interpretation had: **96.6% sensitivity and 94.1% specificity** for the detection of AF as compared with physician-interpreted 12-lead ECGs, with a k coefficient of 0.89 (95% confidence interval 0.82–0.97). **Not-Detected AF:** -Of the 225 simultaneous recordings, 28.8% of ECG-determined AF was not detected by the KMCM algorithm; 91.3% of these were due to “unclassified” recordings by the KMCM algorithm. **Non-interpretable:** Of the 225 simultaneous 12-lead ECG and KMCM recordings, 9 KMCM recordings and 2 ECGs were noninterpretable by the blinded physicians.	Supports aimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients’ daily activities leading to improved patient compliance and data collection.

	3-Physician interpreting sensitivity: Of the remaining 214 simultaneous recordings, physician interpretation of the KMCM recording had 100% sensitivity and 89.2% specificity for the detection of AF as compared with physician-interpreted 12-lead ECGs, with a k coefficient of 0.85 (95% confidence interval 0.78–0.92). -62 recordings were “unclassified” by the KMCM algorithm. Four of the remaining recordings were non-interpretable by the physicians. -Of these 62 “unclassified” recordings, 5 were noninterpretable by the physicians. In the remaining 57 recordings, physician KMCM recording interpretation had 100% sensitivity and 79.5% specificity for the detection of AF as compared with 12-lead ECG interpretation, with a k coefficient of 0.71, a false-positive rate of 20.5%, and a false negative rate of 0% **The sensitivity of KMCM interpretation VS. Physician:** -Of the remaining 159 recordings, KMCM automated algorithm interpretation had **92.4% sensitivity and 97.8% specificity for the detection of AF** as compared with physician-interpreted KMCM recordings, with a k coefficient of 0.91 (95% confidence interval 0.84-0.97) **4-Survey and compliance:** -The majority of patients (93.6%) found the KMCM easy to use, and 59.6% noted that the use of the KMCM subjectively lessened AF diagnosis-related anxiety. Of the survey responders, 63.8% preferred continued use of the KMCM for AF detection.	

	-The KMCM system provides sensitive and specific AF detection relative to 12-lead ECGs when an automated interpretation is provided. -KMCM automated analysis may be a useful adjunct to clinical decision-making for the management of patients with AF. -When the KMCM automated algorithm provides a rhythm interpretation, it can accurately detect AF with very good sensitivity and specificity and excellent inter-observer agreement as compared with 12-lead ECGs. -Direct physician review of KMCM recordings has a strong correlation with that of nearly simultaneously acquired 12-lead ECGs for the detection AF, including instances in which the KMCM algorithm is unable to provide a diagnosis.	
Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation(Hermans et al., 2021)	**Total population:** 115 (91.3%) patients (35 **females**, **median age** 64.0 [58.0–68.0] years) **1-the proportion of patients with recurrent AF Detected:** AliveCor N=29 (25.2%) Holter N=17 (14.8%) (p <0.001) **During the 3-month follow-up**: 12 patients (16.2%) by Holter and 20 patients (27.0%) by AliveCor. **During the 6-month follow-up**: 1 (6.3%) by Holter and 2 (12.5%) by AliveCor. **During the 12-month follow-up**: 4 (16.0%) by Holter and 4 (16.0%) by AliveCor.	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	-In 17 patients AF recurrence was detected by both ACK and Holter. In 12 patients AF recurrence was detected by ACK, but not by Holter ECG. -There was no patient, in whom AF recurrence was detected by Holter ECG only and missed by ACK **2**- Out of115 patients, 61 (53.0%) completed the questionnaires for both the long-term intermittent heart rhythm monitoring **approach by ACK and the short** continuous heart rhythm monitoring approach by Holter, and 72 (62.6%) completed the four-item questionnaire. -Patients graded long-term heart rhythm monitoring by ACK higher (A grade in 40 [65.6%]) as compared to short continuous heart rhythm monitoring by Holter (A grade in 27 [44.3%], p =0.006). - Patients found ACK in the long-term intermittent heart rhythm monitoring approach more convenient in daily usage in comparison to Holter in the short continuous heart rhythm monitoring approach (59 [79.8%] vs 5 [6.8%], p < 0.001) and would recommend the long-term intermittent heart rhythm approach using ACK over the short continuous heart rhythm approach using Holter for arrhythmia monitoring (53 [73.7%] vs 6 [8.4%], p <0.001) **3**- A significant relationship was found between female sex, older age, and thyroid disease, and the number of ECGs taken per day in the long-term intermittent heart rhythm monitoring approach.	

	4-the ACK diagnostic algorithm displayed a sensitivity of 95.3%, a specificity of 97.5%, a positive predictive value of 76.5%, and a negative predictive value of 99.6% for AF detection**.**	
Improving care for patients with atrial fibrillation through the use of a personal electrocardiogram (Praus et al., 2021)	53% **men** (n= 23). **AGE**: 66.7969.78 years (median= 69.00 years; range= 35 years). **Ethnicity**: 77% Caucasian, 10% African American, 8% Hispanic, and 5% Asian. **Residency**: 84% of the patient population resided in the city where the practice is located, 11% in the surrounding area, and5% in a neighboring county, approximately 63 miles west of the city. A total of 1,501 ECG recordings were received and reviewed by the end of eight weeks. **1**- This quality-improvement project provides evidence that implementing the use of a personal, single-lead ECG to manage AF patients is cost-effective and improves patient outcomes while reducing unnecessary resource utilization. Survey: The patient experience and satisfaction surveys were completed by 33 patients (response rate of 77%).	Supports claimed benefits of the technology: • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduce the in-clinic analysis of ECG recordings and reduced outpatient appointments • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.

	2-The majority of patients gave top ratings for the program's ability to decrease anxiety level (62% rated 5). **3**-provide empowerment to manage health concerns (72% rated 5) and increase the ability to communicate with a provider and health care team (84% rated 5).	
Establishing a Smartphone Ambulatory ECG Service for Patients Presenting to the Emergency Department with Pre-Syncope and Palpitations (Reed et al., 2021)	**Total population: 68 patients** **Male**: 30 patients **mean age**: 45.8 years old (SD 15.1) **1**- Asymptomatic cardiac dysrhythmia was detected in six (8.8%) patients. The smartphone ambulatory ECG palpitation service is simple to implement and is effective at detecting cardiac dysrhythmia in emergency and acute palpitation and pre-syncope patients. 2- Three patients had supraventricular tachycardia (SVT; 4%), two had atrial fibrillation (3%), and one had atrial flutter (2%).	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.
Assessment of a standalone photoplethysmography (PPG) algorithm for detection of atrial fibrillation on wristband-derived data (Selder et al., 2020)	**A total** of 180 PPGs and 180 one-lead ECGs were recorded. **mean age:** of 70 ±17 years **1**-AF was identified in 6 (10%) subjects, of which 4 were previously undiagnosed. **2**-Diagnostic performance for AF: (sens/spec/PPV/NPV/acc) -79/98/85/98/96% for the PPG wristband -93/98/81/99/98% for the one-lead ECG wristband	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.

Effect of Smartphone-Enabled Health Monitoring Devices vs Regular Follow-up on Blood Pressure Control Among Patients After Myocardial Infarction (Treskes et al., 2020)	**Total population: 200 patients** (**median age**, 59.7 years [interquartile range {IQR}, 52.9-65.6 years] 156 **men** [78%] **1**-In the intervention group, 79% of patients had regulated BP at 12 months. In the control group, 76%of patients had a regulated BP. This difference was not statistically significant (P = .64). patients were able to accurately measure and transfer BP and a single-lead ECG. **2**-89% patients' satisfaction for the ECG device, **3**-This trial shows that smart technology and e-visits are feasible to implement in the follow-up of low-risk patients after AMI.	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation (Wasserlauf et al., 2019)	**Total population** = 21 patients **Mean age (SD):** 72.1 (7.2) (median: 72.5) **1**-82 episodes of AF ≥1 hour were detected on the ICM while the smartwatch was being worn, of which 80 episodes were detected by the AFSW. **2**--sensitivity of the AFSW for AF episodes ≥1 hour.: (97.5% sensitivity per episode). **3**-The total specificity, PPV, and NPV for detection of AF duration were 98.9%, 76.8%, and 99.9%, respectively.	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.

	These results demonstrate that a commercially available smartwatch with a Food and Drug Administration– cleared ECG sensor, app, and investigational SmartRhythm algorithm is highly sensitive for the detection of AF episodes lasting ≥1 hour in an ambulatory population and for assessment of AF duration when compared with an ICM.	
The Atrial Fibrillation Health Literacy Information Technology System: Pilot Assessment (Magnani et al., 2017)	**Total population:** 31 patients **mean age** of 68 (SD 11) years, 39%= **Woman** -Patients used the relational agent for an average of 17.8 (SD 10.0) days. 1-The mean number of Kardia uses was 26.5 (SD 5.9), and participants using Kardia were in AF for 14.3 (SD 11.0) days. **2**-AFEQT (Atrial Fibrillation Effect on Quality of life) scores improved significantly from 64.5 (SD 22.9) at baseline to 76.3 (SD 19.4) units at 30 days (P<.01). **3**-Marginal but statistically significant improvement in self-reported medication adherence (baseline: 7.3 [SD 0.9], 30 days: 7.7 [SD 0.5]; P=.01). **4**-Assessments of acceptability identified that most of the participants found the relational agent useful, informative, and trustworthy.	Supports claimed benefits of the technology: • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
A Randomized Trial of Pocket-Echocardiography Integrated Mobile Health Device Assessments in Modern Structural Heart Disease Clinics (Bhavnani et al., 2018)	**Total population:** 253 patients -The **mean age** of the study population was 39 +-14 years. -**Woman** = 42%	Supports claimed benefits of the technology: • Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduce the in-clinic analysis of ECG recordings and reduced outpatient appointments.

	-Overall, 34% (85 of 253) of the study population underwent treatment with valvuloplasty or valve replacement on follow-up. **1-**An initial mHealth assessment was associated with a shorter time to referral for valvuloplasty and/or valve replacement (83 +- 79 days vs. 180 +- 101 days; p <0.001) and was associated with an increased probability for valvuloplasty/valve replacement compared to standard-care (34% vs. 32%; adjusted hazard ratio: 1.54; 95% CI: 0.96 to 2.47; p ¼ 0.07). **2**-Patients randomized to mHealth were associated with a lower risk of hospitalization and/or death on follow-up (15% vs. 28%, adjusted hazard ratio: 0.41; 95% CI: 0.21 to 0.83; p ¼ 0.013).	• Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Evaluation of general practitioners' single-lead electrocardiogram interpretation skills: a case-vignette study (Karregat et al., 2020)	**A total** of 1613 KardiaMobile ECGs were interpreted. -The prevalence of AF = 13% **1**-Kardia mobile performance for AF: Sensitivity and specificity for AF was 92.5% (95% CI: 82.5–97.0%) and 89.8% (95% CI: 85.5–92.9%), respectively. **2-**Kardia mobile performance for any abnormalities: In detecting any relevant ECG abnormality (prevalence 22%), sensitivity and specificity were 96.3% (95% CI: 92.8– 98.2%) and 68.8% (95% CI: 62.4–74.6%), respectively. **3-** GPs were able to safely exclude AF/Afl and other relevant ECG abnormalities on a 1L-ECG.	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.

Self-monitoring for recurrence of secondary atrial fibrillation following non-cardiac surgery or acute illness: A pilot study (Lowres et al., 2020)	**Total screened population:** 16,454 patients identifying 224 (1.4%) secondary AF cases Of these, 94 were eligible, and 29 agreed to participate in self-monitoring. (66% **male; median age=** 67 years). Self-monitoring was feasible and acceptable to participants in this setting. 1**-**Sixteen people, who completed the screening intervention, participated in semi-structured interviews at 4-weeks (Supplement All 16 reported the ECG device was easy to use, and time taken to record ECGs was not onerous. The majority (11/16) also reported a sense of security from being able to self-monitor at home, reporting it was ‘‘reassuring” and gave them ‘‘a sense of control”. **2**- 17/29 (59%) participants completed 4-weeks of self-monitoring, 3/29 (10%) completed between 3 and 4 weeks, 2/29 (7%) completed between 1 and 3 weeks, and 6 individuals (21%) completed < 1 week (of these 3 were readmitted to the hospital within 1-week; and 2 withdrew due to dislike of the pop-up advertisements, google games requests, and app update requests that we were unable to disable on the study phone). Participants recorded an ECG a median of 28 days (IQR 10-31), with a median of 3.5 (IQR 1.5-4.5) recordings per day. **3**-Self-monitoring identified AF recurrence in 10 participants (34%; 95% CI, 18% □54%), with	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients’ daily activities leading to improved patient compliance and data collection.

	recurrence occurring 9 days following discharge in 9/10 participants. Only 4 participants (40%) reported associated palpitations with recurrence.	
Nurse-Led Smartphone Electrographic Monitoring for Atrial Fibrillation after Ischemic Stroke: SPOT-AF(Yan et al., 2020)	**The median age** was 66 years (IQR, 55 to 75), 61% = **men** **1**- The nurse-led iECG recordings detected AF in 25 (8.5%) patients, while 24-hour Holter monitoring detected AF in eight (2.8%). AF detection rate by nurse-led iECG recordings was significantly greater than Holter monitoring (McNemar test $\chi 2$ =15.21, P<0.001). **2**- AF was detected in 8.8% (69/785 patients) who underwent iECG recordings only (P=0.8 vs. those who had both iECG and 24-hour Holter). **3-** AF was detected significantly earlier by iECG recordings, at a median of 3 days from stroke onset (IQR, 2 to 6) than for the eight patients who had AF detected by Holter monitoring, in whom AF was detected at a median of 7 days after stroke (IQR, 6 to 10; P=0.02). **4**- At 3 months post-stroke, five of the eight patients detected to have AF on Holter monitoring, had been commenced on anticoagulation therapy, including four of seven patients with AF detection by both methods. A similar proportion of those with AF detected by the nurse-led iECG recordings (11/25) had been commenced on anticoagulation therapy (P=0.4), though numbers are small. Among patients who did not receive Holter monitoring, those with AF detected on the nurse-	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.

	led iECG recordings (n=69), 25 (36%) had been commenced on an anticoagulant at 3 months. The 3-month anticoagulation rate for patients with AF detected by the nurse-led iECG recordings in the Australian centers was 43% (16 of 37) which was higher than in centers in China (20/57, 35%), but this difference was not significant (P=0.4).	
Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study (Halcox et al., 2017)	**Total included Population:** 1004 patients 534= **Female** **Intervention ARM:** Mean Age = 72.6y (5.4) **RC ARM:** Mean Age= 72.6y (5.4) **1- AF Detection:** Nineteen patients in the iECG group were diagnosed with AF during the 12-month study period versus 5 in the RC arm (hazard ratio, 3.9; 95% 95% confidence interval (CI)=1.4–10.4; P=0.007. **2-Comparision of patient's compliance:** There were no significant differences in compliance between those diagnosed with AF (iECG group, n = 19) and those not diagnosed with AF. **3-Patient's satisfaction:** The majority of iECG patients were satisfied with the device, finding it easy to use without restricting activities or causing anxiety.	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Diagnostic Accuracy of a Smartphone-Based Atrial	1-A total of 14,998 ECGs was recorded.	Supports claimed benefits of the technology:

Fibrillation Detection Algorithm (Isma Nusrat Javed 2019)	2- AF was diagnosed in 715 (5%) ECGs, while 1549 (10%) were deemed undetermined by the device. 3-The device had a 99% sensitivity and 98% sensitivity for diagnosing AF.	• Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Preliminary Results of Smartphone Electrocardiogram for Detecting Atrial Fibrillation After A Cerebral Ischemic Event: a Multi-center Randomised Controlled Trial (Koh et al., 2019)	1-Among patients≥55 years of age with a recent cryptogenic stroke or TIA, 30-day smartphone electrocardiogram recording significantly improved the detection of AF as compared with the standard repeat 24-hour Holter monitoring. AF lasting≥30 seconds was detected in 5 out of 38 patients in the intervention group and 0 out of 40 patients in the control group (13.2% vs 0%; absolute difference 13.2%; p=0.024)	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Evaluating smartphone-based photoplesythmography as a screening solution for atrial fibrillation: A digital tool to detect afib? (Grieten et al., 2017)	**Male: 41%** **Mean age: 59±15** **1-The quality performance of two devices:** -AliveCor: 4.3% -Fibrichek: 5.1% **2-The diagnostic capability of the two devices:** -AliveCor: sensitivity100% / Specificity99.6% / Accuracy94.32 -Fibricheck: Sensitivity100% / Specificity97.2% / Accuracy95.4%	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.

Validation study of a pulse-deriving wrist band using spot-check measurements to detect atrial fibrillation (Dankers et al., 2019)	**Total population:** 60 patients **mean age of** 70 ± 17 **male = 32%** **1-The diagnostic performance:** (sens/spec/NPV/PPV) after bad-quality exclusion was: -(72/98/97/81%) for the **ECG wrist band** and -(79/98/98/85) for the **PPG wrist band**	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Comparing a mobile ECG device with Holter monitoring for patients with palpitations in an urgent care setting: a preliminary study (Goel et al., 2018)	**1-Diagnostic yield:** The KM device was diagnostically superior to or concordant with Holter monitoring in 82.0% of patients. **2-Types of detected Arrhythmia:** Arrhythmias detected included atrial and ventricular ectopy, SVT and VT, atrial fibrillation, and inappropriate sinus tachycardia.	Supports claimed benefits of the technology: • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.
iPhone Rhythm Strip: Clinical Implications of Wireless and Ubiquitous Heart Rate Monitoring(Saxon et al., 2012)	**Total population:** 54 Participants **1-Physicians visits:** Use of the device and ECG information caused 24% of subjects to reach out to their private physicians for a consultation and 16% felt that they discovered a health condition unknown to them with the device. **2-**Participants indicated that they found the portability, ease of use, and the form factor to be the design aspects of the device that were most conducive to use. **3-**Transmission interpretation of the 1768 EKGs was normal sinus rhythm (68%); sinus brady or tachy (16%); extra atrial or ventricular systoles (2%); QRS delay	Supports claimed benefits of the technology: • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	(1%); and noise (13%). Symptomatic ventricular tachycardia and asymptomatic ST-segment depression were detected in 2 participants, the latter in Mumbai, India	
Smartphone Enabled ECG Recording Can Scale for the U.S. Heart Failure Ambulatory Population(Bose et al., 2014)	**Total population:** 8,669 persons **1**-Patients were able to record and transmit several ECGs. each, indicating ease-of-use. **2**-Atrial Fibrillation was found in 20.1% of transmissions. **Mean age**: 56 year **Male**: 61%	Supports claimed benefits of the technology: • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Detection of atrial fibrillation on ward rounds with AliveCor ECG in acute ischemic stroke patient(Philip, 2016)	**Total population:** 129 patients **1**-13 (10.1%) were known or were diagnosed to have AF on 12 lead ECG and 20 (15.5%) had AF on AliveCor ECG. **2**- The mobile screening device increased detection of AF by 5.4 %. **3**-Patients with AF had a higher median CHADS2 score compared to non-AF patients [4(2) vs. 3(2), p = 0.005].	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
The role of symptoms in adherence to mHealth ECG monitoring for atrial fibrillation(Reading et al., 2017)	**Total population:** 50 adults **1**-Fifty two percent of iHEART subjects (76% male, mean age 55 +/- 10 years) required frequent reminders (> 3) to transmit their ECG daily over the six-month	Supports claimed benefits of the technology: • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

	monitoring period per protocol. The most commonly reported reason for not transmitting was the absence of symptoms leading patients to assume they were not in AF (without supporting ECG documentation). Yet, 30% of patients who had no symptoms were later found to be in AF and required repeat cardioversion, radiofrequency ablation, or medication adjustment. Interestingly, 66% of participants who transmitted multiple mHealth ECGs (>2 daily) did so only in the setting of symptoms. Shortness of breath and palpitations were the most commonly reported symptoms.	
High Burden of Unrecognized Atrial Fibrillation in Rural India: An Innovative Community-Based Cross-Sectional Screening Program(Soni et al., 2016)	**Total participants:** **133 patients** Almost two-thirds of study participants were 55 years or older, nearly half were female. **1**-Twelve participants screened positive for atrial fibrillation yielding a sample prevalence of 5.1% (95% CI 2.7-8.7) **2**-Mobile technologies may help overcome resource limitations for screening adults for atrial fibrillation in underserved and low-resource settings. **3**-The first screening only identified 7 participants with a positive screen for atrial fibrillation. The remaining 5 participants who screened positive for atrial fibrillation were identified at the fourth screening.	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.
Age-and-sex stratified prevalence of atrial fibrillation in rural Western India: Results of SMART-India, a population-based screening study(Soni et al., 2019)	**Total population:** 2074 participants 1**-**Based on the Kardia's automated algorithm,88 (4.2%) participants had a screening diagnosis of “possible AF”. After clinical adjudication of the iECG tracing,32 individuals were confirmed to have AF. One participant whose heart rhythm was deemed “unclassified” by the	Supports claimed benefits of the technology: • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.

	automated algorithm was classified as AF after clinical adjudication, yielding an overall AF prevalence of1.6% (n = 33). **2**-Two-thirds (22) of those identified as having AF were identified during the first screening, an additional six on the second screening, while the rest on the third screening. **3**-Older participants were more likely to complete all three screenings (p = 0.01) (e-Table 2) and were more likely to have AF (pb0.01) the prevalence of AF among men 65 and older was2-fold higher than the prevalence among women in the same age group (pb0.01).	• Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

(Goldenthal et al., 2019) Recurrent atrial fibrillation/ flutter detection after ablation or cardioversion using the AliveCor KardiaMobile device: iHEART results	
How are the findings relevant to the decision problem?	The study looked at the compliance of AF patients with the daily use of home ECG monitoring and its earlier discovery of recurrent arrhythmia.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Avoiding unnecessary referral to secondary care.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	-A major limitation involved the accuracy of the time to documentation for the control patients, where they were limited to using their EHR to determine the first recurrence. -Also, many control patients did not have documentation of the arrhythmia until they came in for treatment, resulting in an artificially shorter time between discovery and treatment. -This study was also limited by the short duration of the follow-up period. Even though this investigation was randomized and prospective, it has the recognized limitations of a single-centre study.
How was the study funded?	This study was funded by R01 from the National Institute of Nursing Research (R01NR014853).

(Hickey et al., 2017) Evaluating the Utility of Mhealth ECG Heart Monitoring for the Detection and Management of Atrial Fibrillation in Clinical Practice	
How are the findings relevant to the decision problem?	The study looked at the feasibility of the AliveCor ECG for detection of AF/AFL in the real world as well as developed patients' quality of life.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations of this study include the non-randomized ECG assignment and a small homogenous group of subjects.
How was the study funded?	This research is funded by an R01 from the National Institute of Nursing. NIH/NINR R01NR014853.

(Lowres et al., 2016) Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone electrocardiogram	
How are the findings relevant to the decision problem?	The study looked at the feasibility of KardiaMobile for AF detection and also, the role of the device to reduce the anxiety of AF patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Will any information from this study be used in the economic model?	No.

What are the limitations of this evidence?	The main limitation for obtaining diagnostic quality iECGs was the interference caused by poor mobile reception in some rural areas. An additional limitation is that self-monitoring occurred for only 1-month post-discharge; therefore, additional AF recurrences may have been detected if monitoring had been extended past this time.
How was the study funded?	This work was supported by a competitive grant from the Cardiothoracic Surgery Research and Education Fund, Sydney Medical School Foundation, University of Sydney.

(Selder et al., 2019) A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs	
How are the findings relevant to the decision problem?	The study looked at remote monitoring of AF with KardiaMobile and the device performance.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-Firstly, this is a retrospective analysis of a patient population included in the HA program for various reasons and at the discretion of the physician. This may have introduced a substantial selection bias. -As 12-lead ECGs were not available in the present study, specificity data might have been overestimated.
How was the study funded?	Not specified.

(Reed et al., 2019) The IPED (Investigation of Palpitations in the ED) Study: Multi-center Randomized Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED (Investigation of Palpitations in the ED) study.

How are the findings relevant to the decision problem?	The study looked at the usability, effectiveness, and safety of AliveCor technology.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.
Will any information from this study be used in the economic model?	Yes. Informs the economic model parameters related to AF recurrence rate and relative risk of AF recurrence in the intervention arm.
What are the limitations of this evidence?	Potential limitations of the study include a large proportion of recruitment occurring in-office hours largely by research staff in research-active hospitals and the use of a central ECG reading service not available in routine practice.
How was the study funded?	The study was funded by Chest, Heart and Stroke Scotland (Action Research Grant R15/A164; £23,056) and British Heart Foundation (BHF Project Grant no. PG/17/63/33198; £21,347) which included funding for purchasing the devices.

(Rajakariar et al., 2018) Modified positioning of a smartphone-based single-lead electrocardiogram device improves detection of atrial flutter.	
How are the findings relevant to the decision problem?	The study looked at the effect of repositioning of the AliveCor device on improving the AFL detection.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-This is a small validation study with limited patient numbers analysing atrial flutter discrimination from both atrial fibrillation and sinus rhythm. -Altered lead positioning was only performed on patients with a 12 lead ECG diagnosis of atrial flutter. -As the 12 lead and AKM ECGs were not performed concurrently, there is a chance of rhythm variation between tracings.
How was the study funded?	This work was supported by the Eastern Health Foundation Research Grant [EHFRG2017_029].

(Narasimha et al., 2018) Validation of a smartphone-based event recorder for arrhythmia detection	
How are the findings relevant to the decision problem?	The study looked at the usability of the AliveCor device and the diagnostic yield of the device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-The limitations of this study include possible patient selection bias, wherein only English-speaking patients who were relatively familiar with smartphone technology were recruited. -This is a relatively small study, with the majority of patients being younger and without major medical comorbidities. -One other important limitation of the study was the inability to provide 100% real-time monitoring data of the KM rhythm strips.
How was the study funded?	Not specified.

(Tarakji et al., 2015) Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: The iTransmit study	
How are the findings relevant to the decision problem?	The study looked at the feasibility and efficacy of the AliveCor device for the detection of AF.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-At the time of the implementation of the study, the AHM was available only for iPhones, but later new devices were also available for other smartphones. -included all patients who had iPhones irrespective of the frequency of use of smartphones and different applications and irrespective of educational or social background. -TTM is considered as the standard for monitoring results but it could have false readings.
How was the study funded?	Not specified.

(Haberman et al., 2015) Wireless Smartphone ECG Enables Large-Scale Screening in Diverse Populations	
How are the findings relevant to the decision problem?	The study looked at the usability of the AliveCor device on the large scale and also, compared its performance to 12-lead ECG.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	–Demographic data were limited to age, gender, sport (if athlete), and prior history of cardiac disease, and we did not analyse or compare other clinical characteristics. -Populations were samples of convenience and were not randomized. -Sample size was not large enough to have a high likelihood of detecting participants at high risk for SCD. -Healthy young adults also may not be representative of the young adult population on the whole and may tend to have lower cardiac risk secondary to a healthier lifestyle and increased socioeconomic status.
How was the study funded?	Not specified.

(William et al., 2018) Assessing the accuracy of an automated atrial fibrillation detection algorithm using smartphone technology: The iREAD Study

How are the findings relevant to the decision problem?	The study looked at the accuracy of the AliveCor device for the detection of AF.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-This was a single-centre study with a limited sample size. The study population, in this case, had a known history of AF with a burden sufficient to prompt admission for antiarrhythmic drug initiation. Algorithm performance would be expected to vary in a population with a lower AF burden. -All recordings in this study were performed in patients admitted to the hospital. The quality of KMCM recordings may be more variable in patients in the ambulatory setting. -Patients with cardiac implantable electronic devices were not included in this study, and further assessment of the KMCM system is needed in this population. -Patients enrolled in this study had never used the device before. With more experience and frequent use, the quality of the rhythm transmissions may have improved and could affect the automated algorithm interpretation.
How was the study funded?	Not specified.

(Hermans et al., 2021) Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation	
How are the findings relevant to the decision problem?	The study looked at the usability and the effectiveness of the AliveCor device in comparison with Holter monitoring as well as evaluating patients' compliance with the device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.

Will any information from this study be used in the economic model?	Yes.
What are the limitations of this evidence?	-the ACK records only lead I, which can make it difficult to distinguish atrial flutter from sinus rhythm or a regular supraventricular tachycardia, therefore they included all aforementioned arrhythmias in one group “tachycardia”. -Secondly, ACK recordings last only 30 s. If there was an arrhythmia like AF only at the beginning or at the end of the registration, they could not be certain how long this episode lasted which could lead to an underestimation of true AF recurrence rates. -Thirdly, there may be selection bias, as they included only those patients who were willing to use the ACK system. Therefore, there should be caution in generalizing their findings to all patients with AF, as results may differ in other patient populations. -Fourthly, they excluded 11 patients from the study as no recordings were received from them. Usability problems are supposed to
How was the study funded?	This work was supported by Health Foundation Limburg and the RESCAR.

(Praus et al., 2021) Improving care for patients with atrial fibrillation through the use of a personal electrocardiogram	
How are the findings relevant to the decision problem?	The study looked at the effectiveness of the AliveCor device as well as the impact of the device on the reduction of patient’s anxiety.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduce the in-clinic analysis of ECG recordings and reduced outpatient appointments • Ease of use with minimal disruption to patients’ daily activities leading to improved patient compliance and data collection. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-The project involved a single, cardiology practice and may not be representative of patients in other practices or geographic locations. -The KM device has the potential for long-term monitoring; thus, a project with longer follow-up would be needed to examine the use of KM beyond eight weeks. -The KM algorithm interpreted three recordings as possible AF. Upon review, the recordings were noted as sinus rhythm with frequent premature atrial contractions. As previously mentioned, there are many arrhythmias, such as sinus arrhythmia or bundle branch blocks, that are interpreted by the device as “unclassified.” The ability for an NP to review ECGs, interpreted as “unclassified,” is critical to proactive patient care and identifying potentially high-risk arrhythmias. -Patients with movement disorders, such as Parkinson’s disease, may not be able to produce a quality recording because patients must remain stationary for 30 seconds. -The KM device does not have the capability for continuous monitoring beyond a brief time frame; therefore, patients who require observation around-the-clock would necessitate a traditional Holter or a continuous event monitor.
How was the study funded?	M. Proenza obtained funding from Southwest Medical, part of OptumCare for the KardiaMobile devices, and coordinated with Southwest Medical’s IT department.

(Reed et al., 2021) Establishing a Smartphone Ambulatory ECG Service for Patients Presenting to the Emergency Department with Pre-Syncope and Palpitations	
How are the findings relevant to the decision problem?	The study looked at the usability of KardiaMobile in an ambulatory care setting for detection of AF.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile adopted in standard practice, including in rural areas.

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	-The Emergency Medicine Research Group Edinburgh received sponsorship for the EMERGE10 conference in 2018 from various companies including AliveCor. -MR is supported by an NHS Research Scotland Career Researcher Clinician award. The REDCap database used for this study was funded by a Royal College of Emergency Medicine grant.

(Selder et al., 2020) Assessment of a standalone photoplethysmography (PPG) algorithm for detection of atrial fibrillation on wristband-derived data	
How are the findings relevant to the decision problem?	The study looked at the AliveCor device as a reference standard with high accuracy for the detection of AF.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-A first limitation is the relatively small group of subjects. -A second limitation is that this study was conducted in a semi-supervised setting, it is, therefore, unknown whether the algorithm wristband combinations perform the same in an unsupervised home setting for a long-term screening of atrial fibrillation. -A third limitation is the use of a one-lead ECG device with the consensus of two independent experts as the reference instead of a 12-lead ECG. A fourth limitation is the combined use of one specific software algorithm and one specific wristband, other combinations might provide different results.
How was the study funded?	Not funded.

(Treskes et al., 2020) Effect of Smartphone-Enabled Health Monitoring Devices vs Regular Follow-up on Blood Pressure Control Among Patients After Myocardial Infarction	
How are the findings relevant to the decision problem?	The study looked at the feasibility of the AliveCor device to detect AF and its compliance.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-This was a feasibility RCT to evaluate the effects of implementing eHealth in regular care. As such, some design choices were made that might have influenced the course of the trial. First, it was decided that every patient should receive the same smart technology intervention (weight scale, BP monitor, ECG device, and step counter). Every patient was instructed to use the same measurement frequency. This might have influenced measurement adherence and dropout rates in the intervention group, although a certain dropout percentage is frequently observed in RCTs in general. We recognize that this dropout might have influenced patient satisfaction rates because patients who are not satisfied are inherently more likely to drop out. Therefore, patient satisfaction rates should be corroborated in future studies.
How was the study funded?	-Dr. Treskes reported receiving personal fees from Boston Scientific outside the submitted work. -The Department of Cardiology of the Leiden University Medical Center receives unrestricted research and educational grants from Boston Scientific, Medtronic, and Biotronik outside the submitted work. No other disclosures were reported.

(Wasserlauf et al., 2019) Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation	
How are the findings relevant to the decision problem?	The study looked at the accuracy of kardiaband for detection of AF and compared it to the Apple watch.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-First, the smartwatches used in this study had a battery life of ≈24 hours and required daily charging for 1 to 2 hours. Advances in battery technology are expected to improve longevity. -Second, the mean wear time for the smartwatch was 11.3 hours daily, and the majority of individuals chose not to wear the watch while sleeping. Longer wear times may be expected in those individuals when using this technology in a clinical setting. -Third, an AF threshold of ≥1 hour was used for the inclusion of AF episodes in light of several studies suggesting that shorter episodes are not associated with stroke but are associated with high FP rates on ICMs.18,21,25,26 Indeed, when a 30-minute threshold is used in the present study instead of 1 hour, the sensitivity is similar (95.7%) but the PPV decreases to 29.9%. There are no differences in the patient-based analysis. -Fourth, the study evaluated data in only 24 patients. Although the number of true-positive episodes recorded on the AFSW was higher than the number of AF episodes on the ICM. -The AFSW could potentially interpret a single continuous episode of AF as several shorter contiguous episodes due to subjects removing the AFSW during an episode or due to intervening segments of more regular R-R intervals or slower atrioventricular conduction during AF. -Sixth, AFSW accuracy was compared with the ICM as a gold standard, however, the present study demonstrated that not all AF episodes could be correctly detected by the ICM when verified against manual ECG review. -Seventh, only patients with a prior history of paroxysmal AF were included, and the observed accuracy in a screening population may be different.
How was the study funded?	AliveCor provided the KardiaBand monitors, the investigational versions of SmartRhythm and Apple Watches for utilization in the study. AliveCor was not involved in the design, implementation, or data analysis of the study.

(Magnani et al., 2017)

The Atrial Fibrillation Health Literacy Information Technology System: Pilot Assessment	
How are the findings relevant to the decision problem?	The study looked at the usability of KardiaMobile for detection of AF as a smartphone-based relational agent with a high impact on improving patients' quality of life.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-First, the study sample was small (n=31), selected as a convenience cohort, and without randomization. We recognize a biased selection approach that may likely influence our results. For example, individuals recruited for this pilot may be more enthusiastic about the use of new technology, and they, consequently, demonstrate a greater likelihood of daily use than a more generalizable cohort. -Second, individuals received repeated assessments using the same instruments over the 30-day study period. The repeat measurement may modify or influence participant's self-report of HRQoL or medication adherence. – -Third, participants were contacted during the study and offered support using the technology. Participants' use of the intervention may have been influenced by such contact. However, for mHealth to be successful, it must be accessible to users. -Fourth, our limited pilot cohort is racially homogeneous, as only 2 participants belonged to the non-white race. Enhanced recruitment of ethnic and racial minorities—those most likely to experience more severe differences in AF outcomes [62]—is critical to address disparities in AF. -Fifth, we recruited from a limited number of ambulatory sites without control for practice patterns or clinical approaches. There may be residual confounding due to how clinicians caring for such a small-sized cohort may approach AF.
How was the study funded?	This work was supported by Grant 2015084 from the Doris Duke Charitable Foundation. The authors are solely responsible for the design and conduct of this study, all study analyses, as well as the drafting and editing of the manuscript and its final contents.

(Bhavnani et al., 2018)

A Randomized Trial of Pocket-Echocardiography Integrated Mobile Health Device Assessments in Modern Structural Heart Disease Clinics	
How are the findings relevant to the decision problem?	The study looked at the reduction in time of treatment of AF by AliveCor earlier detection time.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduce the in-clinic analysis of ECG recordings and reduced outpatient appointments. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	-We observed unequal sample sizes for 2 main reasons: 1) using an a priori randomization schedule used for daily enrolment versus over the enrolment period; and 2) a simple (or unrestricted) rather than a restricted (i.e., permuted block) randomization method. The simple randomization method allows for random variation in sample sizes important for pragmatic trials and to minimize bias particularly in non–double-blinded studies. In such designs, equal randomization is not necessarily required (33,34). Despite this finding, baseline demographics were well balanced and the overall treatment rates at 12 months were equal between randomized groups, suggesting that bias was minimized when analysing the effectiveness and safety of mHealth. A multiple-arm trial and blinded assessment of pocket echocardiography compared to TTE was not performed as this would be ethically unacceptable because Doppler measurements cannot be performed on pocket devices for accurate hemodynamic assessment required for interventional/surgical referral of cases.
How was the study funded?	The authors thank the American Society of Echocardiography Foundation for program organization, strategic planning, and funding.

(Karregat et al., 2020) Evaluation of general practitioners' single-lead electrocardiogram interpretation skills: a case-vignette study	
How are the findings relevant to the decision problem?	The study looked at the diagnostic accuracy of the AliveCor device and also the accuracy of general practitioners to interpret these results.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-Firstly, selection bias may have been introduced by both our participant selection, all being affiliated with a university medical centre, and the suboptimal response rate. Furthermore, the diagnostic accuracy of incomplete responders tended to be lower compared with complete responders. This may have had a positive effect on our outcomes. -Secondly, we presented the 1L-ECGs rhythm strips to the GPs as 30-s overview files. This may differ from the user experience in a smartphone app where only snippets of a few seconds are shown, and one has to 'swipe' through the rest of the recording. Such a swipe functionality was technically impossible to implement in our questionnaire software. In clinical practice, however, GPs can compute an overview file as a PDF. -Thirdly, we forced respondents to choose from a select number of ECG abnormalities. However, we did give GPs a free text box to enter additional information. Because of this, after study completion, we recoded the open text fields into variables for 'repolarization disorders', 'other relevant findings', and 'doubt'. Finally, since 'any relevant 1L-ECG abnormality' is a composite dichotomous outcome, GPs and cardiologists may have judged a particular 1L-ECG strip as abnormal for different reasons. In such cases, the answer would have been counted as correct, while the underlying interpretation was incorrect.
How was the study funded?	This manuscript was supported by university funds. REH received salary support through a Rubicon grant from the Netherlands Organization of Scientific Research (NWO). The authors report no ties to the manufacturer of the investigated device and had full autonomy in the design, conduct, and reporting of the manuscript.

(Lowres et al., 2020) Self-monitoring for recurrence of secondary atrial fibrillation following non-cardiac surgery or acute illness: A pilot study	
How are the findings relevant to the decision problem?	The study looked at the feasibility and acceptability of the AliveCor device for the detection of AF in a hospital setting.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-The study population may be biased, through self-selection, towards a sample more familiar with using a smartphone. The incidence of secondary AF identified on the wards is likely underestimated due to probable under-reporting of secondary AF episodes and a lack of routine comprehensive screening, thus the sample may be biased towards patients with symptomatic AF. Nursing review of ward lists identified significantly greater numbers with a secondary AF episode than reliance on the ward referring secondary AF episodes to the cardiology team
How was the study funded?	This study was funded by a National Heart Foundation of Australia, Vanguard Grant (101011). Nicole Lowres is funded by a New South Wales Health, Early Career Fellowship (H16/ 52168).

(Yan et al., 2020) Nurse-Led Smartphone Electrographic Monitoring for Atrial Fibrillation after Ischemic Stroke: SPOT-AF	
How are the findings relevant to the decision problem?	The study looked at the feasibility of nurse-led AF monitoring by AliveCor device in a hospital setting and its effectiveness in comparison to 24-h Holter.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Earlier diagnosis and initiation of treatment to control AF or prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	-Firstly, Holter and nurse-led iECG monitoring were not performed simultaneously, because the iECG recordings were restricted to inpatient care, while Holter monitoring was performed either as an

	inpatient or outpatient according to usual practice. However, the aim was to compare an inexpensive nurse-led strategy with routine Holter monitoring according to the usual practice in each stroke unit and was thus a pragmatic study comparing the new strategy with usual care. -Secondly, only a quarter of patients had both 24-hour Holter and iECG recordings, but this reflects usual practice in those stroke units, who would have received no additional monitoring for AF. Moreover, patients diagnosed with AF on iECG may have influenced the decision to additionally use Holter monitoring. This could lead to a selection bias of patients with lower odds of being diagnosed with AF in the Holter group. However, the proportion of patients who received Holter monitoring was identical in both iECG AF positive and negative groups and likewise, the proportion of AF detected on iECG for the Holter and the non-Holter group did not differ.
How was the study funded?	This study was supported by a small grant from Boehringer Ingelheim.

(Halcox et al., 2017) Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study	
How are the findings relevant to the decision problem?	The study looked at earlier detection of AF as well as a reduction in treatment time monitored by the KardiaMobile device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	-population selection bias -The study was not blinded, with electrocardiographic overreads, diagnosis of AF, and determination of clinical outcomes undertaken by the senior physician investigators.
How was the study funded?	The study was funded by a joint grant from the Welsh Government Health Technology and Telehealth Fund and AliveCor Inc.

(Isma Nusrat Javed 2019) Diagnostic Accuracy of a Smartphone-Based Atrial Fibrillation Detection Algorithm	
How are the findings relevant to the decision problem?	Study looked at diagnostic accuracy of KardiaMobile
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

(Koh et al., 2019) Preliminary Results of Smartphone Electrocardiogram for Detecting Atrial Fibrillation After A Cerebral Ischemic Event: a Multi-center Randomised Controlled Trial	
How are the findings relevant to the decision problem?	The study looked at the diagnostic yield of the AliveCor device and compared it to Holter.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.

How was the study funded?	Not specified.

(Grieten et al., 2017) Evaluating smartphone-based photoplesythmography as a screening solution for atrial fibrillation: A digital tool to detect afib?	
How are the findings relevant to the decision problem?	The study looked at the AliveCor device as a reference standard to compare its performance to the Fibricheck device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

(Dankers et al., 2019) Validation study of a pulse-deriving wrist band using spot-check measurements to detect atrial fibrillation	
How are the findings relevant to the decision problem?	The study looked at the feasibility of the AliveCor device for AF detection and its diagnostic performance.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.

How was the study funded?	Not specified.

(Goel et al., 2018) Comparing a mobile ECG device with Holter monitoring for patients with palpitations in an urgent care setting: a preliminary study	
How are the findings relevant to the decision problem?	The study looked at the diagnostic yield of KardiaMobile and compared it to Holter monitoring in urgent care patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved diagnostic accuracy and efficiency in detecting arrhythmias in symptomatic and asymptomatic patients.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

(Saxon et al., 2012) iPhone Rhythm Strip: Clinical Implications of Wireless and Ubiquitous Heart Rate Monitoring	
How are the findings relevant to the decision problem?	The study looked at the usability of the AliveCor device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

(Bose et al., 2014) Smartphone Enabled ECG Recording Can Scale for the U.S. Heart Failure Ambulatory Population	
How are the findings relevant to the decision problem?	The study looked at the performance of the Alivecor device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Improved identification of people with AF, could lead to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke and heart failure.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

Detection of atrial fibrillation on ward rounds with AliveCor ECG in acute ischemic stroke patient(Philip, 2016)	
How are the findings relevant to the decision problem?	The study looked at the diagnostic performance of the device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

(Reading et al., 2017) The role of symptoms in adherence to mHealth ECG monitoring for atrial fibrillation	
How are the findings relevant to the decision problem?	The study looked at the adherence of patients to the AliveCor device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Not specified.
How was the study funded?	Not specified.

(Soni et al., 2016) High Burden of Unrecognized Atrial Fibrillation in Rural India: An Innovative Community-Based Cross-Sectional Screening Program	
How are the findings relevant to the decision problem?	The study looked at the Feasibility of AliveCor device for detection of AF.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	First, this study is based on a relatively small sample size of 235 participants. Second, they did not perform a gold standard 12-lead ECG to confirm the positive screening findings. It is important to note, however, that AliveCor devices are FDA-approved and are widely used by cardiologists in diverse clinical settings.

	Third, the cross-sectional study design limits the ability to assess any potential outcomes associated with atrial fibrillation or characterize the clinical presentation of atrial fibrillation in more detail.
How was the study funded?	Soni A. received support from the National Center for Advancing Translational Sciences (TL1-TR001454), and JA received support from the National Institute on Minority Health and Health Disparities (P60-MD006912-05). DDM's time was supported by KL2RR031981, 1R15HL121761-01A1, 1UH2TR000921-02, and 1R01HL126911-01A1 from the National Heart, Lung, and Blood Institute.

(Soni et al., 2019) Age-and-sex stratified prevalence of atrial fibrillation in rural Western India: Results of SMART-India, a population-based screening study	
How are the findings relevant to the decision problem?	The study looked at the prevalence of AF screened by AliveCor device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Improved identification of people with atrial fibrillation (AF), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	1-findings are based on a single-lead iECG recording collected using an FDA-approved device, whereas the gold-standard for the diagnosis of AF has usually been thought to be a 12-lead ECG. However, the approach was consistent with recommendations enumerated in the most recent consensus document endorsed by four major international entities for heart rhythm societies. 2-Although clinical adjudication of single-lead iECG is widely accepted as a screening and clinical decision-making strategy, they do not present results of a further cardiovascular evaluation of participants in this manuscript because clinical follow-ups are ongoing. This lack of more detailed clinical evaluation and follow-up which was beyond the scope of this study limits the ability to present the outcomes of AF detection including rates of

	OAC prescription, OAC adherence, or stroke/bleeding rate among screen-positive participants .
How was the study funded?	This study was supported by the 2016 University of Massachusetts Medical School Office of Global Health Pilot Project Award through institutional grant (UL1-TR001453).

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

A search of the Medicine and Healthcare Products Regulatory Agency (MHRA) website (11th March 2021) showed no manufacturer field safety notices or medical device alerts have been issued for Kardia/KardiaMobile/AliveCor/Kardiaband/KM (https://www.gov.uk/drug-device-alerts).

AliveCor, Inc. has received US FDA 510(k) clearance for the KardiaMobile with a classification product code "DXH" (Transmitters And Receivers, Electrocardiograph, Telephone) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K191406).

The search of the FDA recall database (11th March 2021) with the terms "KardiaMobile", "Kardia", "AliveCor", "Kardiaband" and "KM" returned one result in which the reason for the recall was: AliveCor ECG App version 2.1.2 crashed upon the use of the application. AliveCor posted information on their website, Facebook page, and Twitter to alert users of the issue. This recall was not related to the KardiaMobile device itself. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=133315)

A search of the FDA adverse databases (MAUDE, MDR, and MedSun) with search dates from 1976 to 11th March 2021 using the product code "DXH" and, or "AliveCor" identified 5 records and three of them were user's fault, and patients did not experience an adverse event. Two of them were not responded to by the manufacturer. Therefore, we can conclude that the device is safe when used and intended.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

There is no reported adverse event reported in published clinical studies.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

The included studies were not homogeneous in terms of the study design and the comparators and patient population therefore we did not conduct any meta-analysis

Report all relevant results, including diagrams if appropriate.

Not applicable

Explain the main findings and conclusions drawn from the evidence synthesis.

Not applicable

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

The included studies were not homogeneous in terms of the study design and the comparators and patient population therefore it was impractical to conduct any meta-analysis. Therefore, The overall results of the 33 included studies are summarised as below: 1- (Goldenthal et al., 2019): In this study, pieces of evidence have supported that when AF patients are compliant with daily use of home ECG monitoring, recurrent arrhythmias are discovered earlier when compared to control patients. Results suggest that the AliveCor KardiaMobile home

monitoring device is mostly beneficial for prompt detection of early (first month) recurrence. This can empower patients and providers to make informed health decisions and develop treatment plans sooner.

2-(Hickey et al., 2017): Atrial Fibrillation self-monitoring with the AliveCor™ ECG device is a feasible and effective mechanism for improving AF/AFL detection (more than twice AF detection) in the real-world setting. Diagnosed patients with AF who followed self-monitoring and knew their ECGs were vigilantly reviewed reported a better self-reported quality of life.

3-(Lowres et al., 2016): Attaching an iECG case to a smartphone is a non-invasive, inexpensive, convenient, and feasible screening method for AF recurrence in patients undergoing cardiac surgery and no prior history of Atrial Fibrillation. It also provides information about the condition and potentially reduces anxiety.

4-(Selder et al., 2019): The present study shows the first remote monitoring arrhythmia program in the Netherlands with more than 90% of the interpretable ECGs. Although the Kardiamobile algorithm provides a high negative predictive value, positive predictive values are relatively low. The manual assessment of all ECGs categorized as other than normal sinus rhythm is required. However, Utilizing the device for interpretation of arrhythmias of unknown origin, all ECGs should be manually evaluated since non-AF arrhythmias (including ectopy) are poorly recognized by the algorithm and may be classified as normal sinus rhythm.

5-(Reed et al., 2019): This study demonstrates the ability of the KardiaMobile to boosts clinical care and patient experience for those suffering undiagnosed palpitations and pre-syncope in comparison to standard care group (increased the number of patients in whom an ECG was captured during symptoms over five-fold to more than 55% at 90 days).

6-(Rajakariar et al., 2018): The current study shows that Kardiamobile algorithm interpretation of results is comparable to standard care. However, the device's repositioning to create a lead-II trace resulted in a notable enhancement in clinician diagnosis of AFL. On the other hand, the inconvenient position of this technique limits the device's feasibility for screening. Nevertheless, this modified positioning may be considered in high-risk groups to improve AFL detection.

7-(Narasimha et al., 2018): The Kardiamobile is equivalence to a standard long-term external ELR for the diagnosis of arrhythmias by providing accurate, reliable real-time data to both patients and healthcare providers that can be accessed easily and rapidly. Due to smartphones' worldwide use, a device is an attractive option for the initial diagnosis of palpitations in stable, relatively low-risk patients.

8-(Tarakji et al., 2015): This study shows a comparable performance of KardiaMobile to conventional methods for monitoring patients after the AF ablation procedure, with 100% sensitivity and 97% sensitivity in the detection of AF and atrial flutter. Generally, patients find the device easy to use, and a large majority of them preferred to use the device rather than traditional monitoring.

9-(Haberman et al., 2015): This study provided further evidence that Kardiamobile can be used for large-scale screening to detect conduction intervals and common arrhythmias such as AF. Effective algorithm interpretation and decision support are features that make this device incorporated for real-word setting screening of AF.

10-(William et al., 2018): Kardiamobile automated analysis is a useful adjunct to clinical decision-making to manage patients with AF. The device provides comparable diagnostic performances for AF detection when the device automated algorithm shows a valid interpretation with high sensitivity and specificity to the 12-lead ECGs. Direct physician review of the device recordings has a

significant correlation with that of nearly simultaneously acquired 12-lead ECGs for the detection AF, including instances in which the KMCM algorithm cannot provide a diagnosis.

11-(Hermans et al., 2021): In this study, four weeks of long-term intermittent heart rhythm monitoring by Kardiamobile identified more patients with AF recurrences after AF ablation than short continuous heart rhythm monitoring by Holter ECG. Kardiamobile displayed a high diagnostic accuracy, as well as having higher patient usability as compared to Holter. This will make the device capable of detecting AF in long-term follow-ups potentially.

12-(Praus et al., 2021): This project provides evidence that utilizing Kardiamobile to manage AF patients is cost-effective and improves patient outcomes while reducing unnecessary resource utilization. Moreover, patient's anxiety related to their AF is reduced. Most importantly, patients feel they have better access to their cardiology providers, and patients living in isolated areas, or traveling to other cities and countries, can be managed remotely.

13-(Reed et al., 2021): This study showed that Kadiamobile ambulatory ECG palpitation service is straightforward to implement and effectively detect cardiac dysrhythmia in emergency and acute palpitation pre-syncope patients. This is the first report anywhere of an ambulatory smartphone palpitation service.

14-(Selder et al., 2020): This feasibility study demonstrates Kardiamobile as a reference standard device for detecting AF and compared it with the Fibricheck device's performance as a novel AF detection technique. The Fibricheck device shows comparable results to the Alivecor Kardia one-lead ECG device and its algorithm on the user level. The performance of Kardiamobile is high with 100% sensitivity and 98% specificity.

15-(Treskes et al., 2020): Follow-up using smart technology(Kardiamobile is a sub-group of this technology) for patients with Myocardial infarction did not yield different percentages of regulated BP compared with patients who received standard care. This trial shows that smart technology and e-visits are feasible to implement in the follow-up of low-risk patients after Myocardial infarction. Patient satisfaction and clinical outcomes in this instance were similar.

16-(Wasserlauf et al., 2019): This study had compared the accuracy of Kardiaband with an insertable cardiac monitor(ICM). Kardiaband is highly sensitive (97.7%) for detecting AF and assessing AF duration in an ambulatory population compared with an ICM. Such devices may represent an inexpensive, noninvasive approach to long-term AF surveillance and management.

17-(Magnani et al., 2017): This study presented results on the pilot use of Kardiamobile. In this limited-sized study conducted over 30 days, strong adherence to the device has been identified and showed significant improvements in patient's quality of life(AFEQT scores improved significantly from 64.5 (SD 22.9) at baseline to 76.3 (SD 19.4) units at 30 days). Participants found the device acceptable, useful, informative, and trustworthy.

18-(Bhavnani et al., 2018): This study depicted the effectiveness of Kardiamobile to prevent patients from sequels which may be caused due to delayed time of treatment. Compared to standard care, an initial testing strategy with Kardiamobile was associated with a shorter referral time for treatment among symptomatic patients with advanced Structural heart disease SHD. It improved health outcomes in an endemic area with a high burden of disease.

19-(Karregat et al., 2020): This study revealed that health care providers(General practitioners) could safely diagnose cardiac arrhythmias, including AF, using Kardiamobile. However, when an ECG abnormality is suspected, the GP is incorrect in half of the cases. An automatic ECG interpretation algorithm for AF did not improve GPs' diagnostic accuracy. As such, whenever the

GP or the algorithm suspects an abnormality, a low threshold for consulting an ECG expert for confirmation of this abnormality is recommended.

20-(Lowres et al., 2020): The current data suggest approximately 1-in-3 patients who experience transient secondary AF following non-cardiac surgery and who are discharged in sinus rhythm will have recurrent AF early after discharge. These recurrent episodes are often asymptomatic but can be detected promptly and easily using patient self-monitoring by Kardiamobile. This data suggest prophylactic anticoagulation therapy for most patients with recurrent AF have a risk of thromboembolic complications.

21-(Yan et al., 2020): This study showed that a nurse-led strategy of intermittent hand-held iECG recordings by Kardiamobile device as part of collection of routine vital signs in the post-stroke period in hospital detected new PAF in 8.5% of patients, significantly more, and significantly earlier post-stroke than routine 24-hour Holter monitoring performed in only 27% of patients. Nurse-led smartphone-enabled intermittent cardiac monitoring with the Kardia device could be considered complementary to standard routine post-stroke investigations for AF or could even replace routine 24-hour Holter monitoring as a scalable, low-cost solution which could be widely implemented in countries with diverse availability of health resources to increase the yield of AF detection early after stroke or TIA.

22-(Halcox et al., 2017): This study suggests that regular twice-weekly iECG screening by Kardiamobile is highly acceptable to the elderly population (people >65 years of age) at increased risk of AF and stroke and results in an almost 4-fold increase in the diagnosis of AF over a year. These results showed a high AF detection rate and a lower incidence of ischemic strokes/ TIAs resulting from AF or undetermined achieved with this monitoring strategy.

23-(Isma Nusrat Javed 2019): The Kardiamobile ECG device provides excellent diagnostic accuracy in diagnosing AF, supporting the notion that such a device can be used for AF screening. In this setting, high sensitivity in diagnosing AF will allow physicians to review only those recordings that are classified by the device as AF to decrease the burden of having to review every transmitted ECG recording. The diagnostic accuracy of this single-lead ECG device is critically dependent on high-quality signals.

24-(Koh et al., 2019): The result of this abstract showed that among patients ≥55 years of age with a recent cryptogenic stroke or TIA, 30-day smartphone electrocardiogram recording by Kardiamobile significantly improved the detection of AF as compared with the standard repeat 24-hour Holter monitoring. However, there was no change in clinical practice in response to the detection of AF.

25-(Grieten et al., 2017): The results of This abstract showed the Kardiamobile as a reference standard for AF detection to compare other novel devices in this regard. (Alivecor Kardiamobile showed 100% sensitivity and 99.6% specificity for detection of AF.) Using a smartphone application based on PPG in a screening setting resulted in good results compared to a single-lead ECG device.

26-(Dankers et al., 2019): This feasibility study demonstrates the Kardiamobile as a reference to evaluate the other novel technologies in detecting AF(Kardiamobile showed 83% sensitivity and 98% specificity). The opportunity to use wearable technologies for the detection and screening of atrial fibrillation. The optical PPG technology showed comparable results to the current state-of-the-art single lead ECG Kardiamobile devices.

27-(Goel et al., 2018): This abstract showed that the KardiaMobile is a cost-efficient device that can be used to screen urgent care patients with palpitations. In most patients, it determines whether a

further cardiac investigation is required. The Kardiamobile device is diagnostically superior to Holter monitoring in 82% of patients.

28-(Saxon et al., 2012): Anytime ECG monitoring by Kardiamobile device, as an adjunct to a smartphone, is intuitive and allows users to learn about and characterize their heart rates & rhythms. It provides global identification of arrhythmias at any time. The implications of this technology for improving public awareness of health metrics and the early diagnosis of arrhythmias are enormous. Self-monitoring with this device doesn't need special training, and subjects used the case conveniently to record the ECG.

29-(Bose et al., 2014): This abstract showed that utilizing Kardiamobile provides patients with the ability to record ECGs easily and allows the potential to radically disrupt the way cardiac screening, diagnosis, and monitoring is performed for U.S. heart failure patients. This AF screening method can easily be scaled in the U.S. and globally.

30-(Philip, 2016): AF screening with a handheld tool (Kardiamobile device) during regular ward rounds improves the detection rate and early treatment of patients with acute ischemic stroke. The mobile screening device increased the detection of AF by 5.4 %. Patients with AF on AliveCor ECG compared to no AF had severe baseline deficits.

31-(Reading et al., 2017): This abstract showed that Cardiac mHealth self-monitoring (Kardiamobile) by patients is a feasible and effective mechanism for detecting AF. However, most patients required frequent reminders (> 3) to transmit their ECG daily over the six-month monitoring period.

32-(Soni et al., 2016): This study suggests a prevalence of atrial fibrillation in the special Indian region which detected by the Kardiamobile device (5.1%) that is markedly higher than has been previously reported in India and similar to the prevalence estimates reported in studies of persons from North America and Europe. The historically low reported burden of atrial fibrillation among individuals from low and middle-income countries may be due to a lack of routine screening. KardiaMobile may help overcome resource limitations for atrial fibrillation screening in underserved and low-resource settings.

33-(Soni et al., 2019): These results from the SMART-India study disrupt the conventional wisdom about AF's epidemiology in India by demonstrating a three-fold higher rate of AF than has been previously reported, most of which had not previously diagnosed. This study also presents a road map for a community-based targeted AF screening program by utilizing the Kardiamobile device, which can help identify patients with AF who are at high risk for experiencing an adverse event. Furthermore, it is recommended that increasing the screening to twice or more will enhance the detection of AF among the population.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

Detection of atrial fibrillation utilizing the AliveCor monitoring device has been shown to increase the number of detected AF among high-risk patients. Evidence supporting the comparable effectiveness of AliveCor device and Gold standard diagnostic methods such as Holter monitoring or 12-Lead ECGs. Furthermore, some evidence confirmed that even AliveCor device had higher diagnostic performance than Gold standard methods and depicted an improved AF identification. (This evidence includes 16 published studies and four abstracts which were included in the critical literature appraisal.

The feasibility of detecting AF by employing the AliveCor device in real-world population have been authenticated in the evidence which means that large populations, as well as Populations in a rural area with limited access to hospital diagnostic settings, may benefit from AliveCor device (A total of 13 published and two abstracts demonstrated these benefits).

No AliveCor/KardiaMobile-related adverse events were found in searches of the MHRA and FDA databases or reported in any of the clinical studies identified. (As the KardiaMobile is an external non-invasive device performing by using two fingers of each hand and only 30 seconds.)

Earlier detection of AF will lead to earlier initiation of treatment, which will also decrease the number of hospitalizations. As supported by the studies (six published studies), earlier diagnosis and initiation of treatment would control AF or prevent the occurrence of clinical sequelae or arrhythmias such as syncope, stroke, and heart failure.

Given the Gold standard devices' inconvenient monitoring, KardiaMobile and its Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection .13 studies verified that patient’s satisfaction was significantly higher using KardiaMobile device than using Gold standard methods or other devices. On the other hand, the patient's quality of life following the KardiaMobile device's use has been improved significantly, and the patient's anxiety level was notably reduced.

According to the clinical effectiveness of KardiaMobile, intervention leads to cost-saving not only for the patients but also for the healthcare system. Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The collective evidence base includes studies of the KardiaMobile AliveCor device, supporting published literature related to the detection of Atrial Fibrillation and clinical practice guidelines involving detection of Atrial Fibrillation.

The relevance of this evidence to the scope is provided below.

- KardiaMobile/AliveCor device Evidence: 24 Published manuscripts and 9 published abstracts/posters
- These studies were conducted in the UK as well as major markets with similar population characteristics and standards of care such as the USA, The Netherlands, Australia, and Canada.
- Patients included in the studies were those with known AF, at risk for AF as well as healthy populations.
- Confirming the AliveCor device performance as an alternative or adjunct to routine standard of diagnosis, a great number of studies were collected in real-world use setting.
- The majority of Control groups in those comparative trials involved Gold standards such as 12-Lead ECGs and 24h-Holter monitoring.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

None known.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The KardiaMobile device is intended to record, store and transfer ECG rhythms for patients with a history or risk of Atrial fibrillation such as elderly population, presence of heart disease, presence of high blood pressure, drinking alcohol, and obese patients.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

-Strengths:

- A large number of studies focusing on the diagnostic effectiveness of the KardiaMobile device have been identified (16 published, 4 abstract, 3 ongoing)

- A large number of studies indicated the feasibility of AF detection by KardiaMobile device (11 published, 2 abstract, 6 ongoing)
- A majority of the evidence is collected in real-world settings.
- The countries in which studies have been conducted are varied (USA, UK, The Netherlands, Australia, India, Canada, Belgium, Poland, and China), allowing for an understanding of potential diagnostic impact in a wide range of settings.
- All studies which have focussed on device performance and accuracy as an outcome have reported favourable results for the KardiaMobile device. In many cases, results were significant and clinically meaningful.
- In those studies that reported on Time of diagnosis as well as the time of treatment, there was a significant reduction in time of diagnosis and treatment.
- Potential economic benefits of utilizing KardiaMobile devices for detection of AF have been reported in published studies.
- In those studies, assessing the quality of life of patients who utilized the KardiaMobile device, there was a notable increase in their quality of life.

-Limitations:

- Certain studies highlighted a small sample size included as being a drawback of the study ((Goldenthal et al., 2019), (Hickey et al., 2017), (Rajakariar et al., 2018), (Narasimha et al., 2018), (Haberman et al., 2015), (William et al., 2018), (Selder et al., 2020), (Magnani et al., 2017))
- Certain studies reported on the lack of long-term follow up((Praus et al., 2021))
- Certain studies mentioned the single centre design as being a disadvantage of the study.((Goldenthal et al., 2019), (William et al., 2018), (Praus et al., 2021))
- Certain studies reported absence of randomized assignment as being a limitation of the analysis.((Hickey et al., 2017), (Haberman et al., 2015), (Magnani et al., 2017).
- Certain studies reported patient selection bias as being downside of the study.((Narasimha et al., 2018), (Hermans et al., 2021), (Magnani et al., 2017), (Karregat et al., 2020), (Lowres et al., 2020), (Halcox et al., 2017))
- Certain study reported inability of KardiaMobile utilization in patients with movement disorders such as Parkinson as a limitation of the study. ((Praus et al., 2021)).

9 References

Please include all references below using NICE's standard referencing style.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	February 05, 2021
Date span of search:	See date span of search in search strategies below.

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Database: PUBMED (All fields) <To February 05, 2021>		Result
#1	((((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR (non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)	88,552 results
#2	((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro)	19,879 results
#1 AND #2	((((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR (non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)) AND ((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro))	584

Database: EMBASE (All fields, <To February 05, 2021>)		Result
#1	'atrial fibrillation'/exp OR 'atrial fibrillation' OR 'atrium fibrillation' OR 'auricular fibrilation' OR 'auricular fibrillation' OR 'cardiac atrial fibrillation' OR 'cardiac atrium fibrillation' OR 'fibrillation, heart atrium' OR 'heart atrial fibrillation' OR 'heart atrium fibrillation' OR 'heart fibrillation atrium' OR 'non-valvular atrial fibrillation' OR 'nonvalvular atrial fibrillation' OR 'paroxysmal atrial fibrillation'/exp OR 'paroxysmal atrial fibrillation' OR 'paroxysmal heart atrium fibrillation' OR 'persistent atrial fibrillation'/exp OR 'persistent atrial fibrillation' OR 'persistent atrium fibrillation' OR 'persistent heart atrium fibrillation' OR 'new-onset atrial fibrillation'/exp OR 'acute atrial fibrillation' OR 'acute heart atrium fibrillation' OR 'new-onset atrial fibrillation' OR 'recent-onset atrial fibrillation'	179,812
#2	'KardiaMobile'/exp OR 'kardia mobile'/exp OR 'AliveCor'/exp OR 'self-recording ecg' OR 'KardiaMobile 6l' OR 'mobile monitoring' OR 'single lead ecg' OR 'portable single lead ecg' OR 'single lead ecg recorder' OR 'portable single lead ecg recorder' OR 'wearable rhythm recording' OR 'kardia'/exp OR 'zenicor ecg' OR kardiapro OR kardiaapp OR 'kardia app'	729
#1 AND #2	('KardiaMobile'/exp OR 'kardia mobile'/exp OR 'AliveCor'/exp OR 'self-recording ecg' OR 'KardiaMobile 6l' OR 'mobile monitoring' OR 'single lead ecg' OR 'portable single lead ecg' OR 'single lead ecg recorder' OR 'portable single lead ecg recorder' OR 'wearable rhythm recording' OR 'kardia'/exp OR 'zenicor ecg' OR kardiapro OR kardiaapp OR 'kardia app') AND ('atrial fibrillation'/exp OR 'atrial fibrillation' OR 'atrium fibrillation' OR 'auricular fibrilation' OR 'auricular fibrillation' OR 'cardiac atrial fibrillation' OR 'cardiac atrium fibrillation' OR 'fibrillation, heart atrium' OR 'heart atrial fibrillation' OR 'heart atrium fibrillation' OR 'heart fibrillation atrium' OR 'non-valvular atrial fibrillation' OR 'nonvalvular atrial fibrillation' OR 'paroxysmal atrial fibrillation'/exp OR 'paroxysmal atrial fibrillation' OR 'paroxysmal heart atrium fibrillation' OR 'persistent atrial fibrillation'/exp OR 'persistent atrial fibrillation' OR 'persistent atrium fibrillation' OR 'persistent heart atrium fibrillation' OR 'new-onset atrial fibrillation'/exp OR 'acute atrial fibrillation' OR 'acute heart atrium fibrillation' OR 'new-onset atrial fibrillation' OR 'recent-onset atrial fibrillation')	**191**

Database: COCHRANE (All fields, <To February 05, 2021>)		Result
#1	((KardiaMobile) OR (Kardia mobile) OR (Kardiaband) OR (Kardia band) OR (Kardiaapp) (Word variations have been searched) OR (AliveCor) OR (KardiaMobile 6l) OR (Self-recording ECG) OR (Mobile AF) OR (Mobile monitoring) (Word variations have been searched) OR (Single lead ECG) OR (Portable single lead ECG) OR (Single lead ECG recorder) OR (Portable single lead ECG recorder) OR (Wearable rhythm recording))	5675
#2	((atrial fibrillation) OR (auricular fibrillation) OR (cardiac atrial fibrillation) OR (heart atrium fibrillation) OR (nonvalvular atrial fibrillation) OR (chronic atrial fibrillation) OR (paroxysmal atrial fibrillation) OR (permanent atrial fibrillation) OR (persistent atrium fibrillation) OR (acute atrial fibrillation))	13446
#1 AND #2	(((atrial fibrillation) OR (auricular fibrillation) OR (cardiac atrial fibrillation) OR (heart atrium fibrillation) OR (nonvalvular atrial fibrillation) OR (chronic atrial fibrillation) OR (paroxysmal atrial fibrillation) OR (permanent atrial fibrillation) OR (persistent atrium fibrillation) OR (acute atrial fibrillation))) AND (((KardiaMobile) OR (Kardia mobile) OR (Kardiaband) OR (Kardia band) OR (Kardiaapp) (Word variations have been searched) OR (AliveCor) OR (KardiaMobile 6l) OR (Self-recording ECG) OR (Mobile AF) OR (Mobile monitoring) (Word variations have been searched) OR (Single lead ECG) OR	**253**

	(Portable single lead ECG) OR (Single lead ECG recorder) OR (Portable single lead ECG recorder) OR (Wearable rhythm recording)))	

Database: ICTRP (All fields, All fields, <To February 05, 2021>)		Result
#1	KardiaMobile OR kardia mobile OR AliveCor OR self-recording ecg OR KardiaMobile 6l OR mobile monitoring OR single lead ecg OR portable single lead ecg OR single lead ecg recorder OR portable single lead ecg recorder OR wearable rhythm recording OR kardia OR zenicor ecg OR kardiapro OR kardiaapp OR kardia app.	**202**

Database: Clinicaltrials.gov (All fields, <To February 05, 2021>)		Result
#1 Condition	atrial fibrillation OR atrial fibrillation OR atrium fibrillation OR auricular fibrillation OR auricular fibrillation OR cardiac atrial fibrillation OR cardiac atrium fibrillation OR fibrillation, heart atrium OR heart atrial fibrillation OR heart atrium fibrillation OR heart fibrillation atrium OR non-valvular atrial fibrillation OR nonvalvular atrial fibrillation OR paroxysmal atrial fibrillation OR paroxysmal atrial fibrillation OR paroxysmal heart atrium fibrillation OR persistent atrial fibrillation OR persistent atrial fibrillation OR persistent atrium fibrillation OR persistent heart atrium fibrillation OR new-onset atrial fibrillation OR acute atrial fibrillation OR acute heart atrium fibrillation OR new-onset atrial fibrillation OR recent-onset atrial fibrillation	2558
#2 device	KardiaMobile OR kardia mobile OR AliveCor OR self-recording ecg OR KardiaMobile 6l OR mobile monitoring OR single lead ecg OR portable single lead ecg OR single lead ecg recorder OR portable single lead ecg recorder OR wearable rhythm recording OR kardia OR zenicor ecg OR kardiapro OR kardiaapp OR kardia app.	2162
#1 AND #2	KardiaMobile OR kardia mobile OR AliveCor OR self-recording ecg OR KardiaMobile 6l OR mobile monitoring OR single lead ecg OR portable single lead ecg OR single lead ecg recorder OR portable single lead ecg recorder OR wearable rhyth | atrial fibrillation OR atrial fibrillation OR atrium fibrillation OR auricular fibrillation OR auricular fibrillation OR cardiac atrial fibrillation OR cardiac atrium fibrillation OR fibrillation, heart atrium OR heart atrial fibrillation	**122**

Database: Web of sciences (All fields, <To February 05, 2021>)		Result
#1	ALL FIELDS: (atrial fibrillation OR atrium fibrillation OR auricular fibrillation OR cardiac atrial fibrillation OR cardiac atrium fibrillation OR fibrillation, heart atrium OR heart atrial fibrillation OR heart atrium fibrillation OR non-valvular atrial fibrillation OR paroxysmal atrial fibrillation OR persistent atrial fibrillation OR new-onset atrial fibrillation OR acute atrial fibrillation OR new-onset atrial fibrillation) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI* *Timespan=All years*	103,570
#2	ALL FIELDS: (KardiaMobile OR kardia mobile OR AliveCor OR self-recording ecg OR KardiaMobile 6l OR single lead ecg OR portable single lead ecg OR single lead ecg recorder OR portable single lead ecg recorder OR wearable	2,768

	rhythm recording OR kardia OR zenicor ecg OR kardiapro OR kardiaapp OR kardia app) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI* *Timespan=All years*	
#1 AND #2	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI* *Timespan=All years*	**480**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Enter text.

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Adult populations (>18 years) with suspected Cardiac arrhythmias including AF require diagnosis and monitoring (e.g., palpitations investigation).
Interventions	Studies with KardiaMobile as the intervention or comparator.
Comparator	The comparators are the current diagnostic pathway for ambulatory cardiac arrhythmia detection as per NICE clinical guidelines for the diagnosis of atrial fibrillation.
Outcomes	Any studies regarding that tested the function of KardiaMobile in AF patients.
Study design	All types of study designs and abstracts.
Language restrictions	No language restriction.
Search date	No restriction.
Exclusion criteria	
Outcomes	Costs and cost-effectiveness analysis, Screening only, Single time point testing, economic models, Not right population, Not reported the device name as intervention or comparator, studies in pediatrics
Study design	Animal studies, In vitro studies, case-reports, Editorial/commentary, Systematic Review and Meta-Analysis, Letters, Book chapters.

Data abstraction strategy:

Data from all included studies were extracted using pre-designed form. Data extraction was undertaken by one reviewer and checked by a second independent reviewer. Disagreements between the review authors were solved by discussion, and the consensus was reached with the involvement of a third review author where necessary.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full-text review but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
The Heart Rhythm Society/American College of Physicians Atrial Fibrillation Screening and Education Initiative	Feasibility study	Screening Only	Text
Screening for Atrial Fibrillation Using Economical and Accurate Technology (From the SAFETY Study)	Case control study	Screening Only	Text
Screening for atrial fibrillation in 13 122 Hong Kong citizens with smartphone electrocardiogram	Feasibility study	Screening Only	Text
Diagnostic Performance of a Smartphone-Based Photoplethysmographic Application for Atrial Fibrillation Screening in a Primary Care Setting	Prospective observational study	Screening Only	Text
iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke.	Editorial	Screening Only	Text
The in-ear region as a novel anatomical site for ECG signal detection: validation study on healthy volunteers	Validity study and Feasibility	Screening Only	Text
Accuracy of a smartwatch based single-lead electrocardiogram device in detection of atrial fibrillation	A prospective multicenter validation study	Single time point	Text
Using mobile ECG devices to increase detection of atrial fibrillation across a range of settings in south London	Observational / cross-sectional study	Single time point	
Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-center, clinical validation study (DETECT AF PRO).	Prospective two-center validation study	Single time point	
The effectiveness of a mobile ECG device in identifying AF: sensitivity, specificity and predictive value	Feasibility study	Single time point	
Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting	Nonrandomised observational study	Single time point	
Kardia Mobile applicability in clinical practice: A comparison of Kardia Mobile and standard 12-lead electrocardiogram records in 100 consecutive patients of a tertiary cardiovascular care center	Observational validation study	Single time point	
Diagnostic Accuracy of a Smartphone-Operated, Single-Lead	Observational validation study	Single time point	

Electrocardiography Device for Detection of Rhythm and Conduction Abnormalities in Primary Care			
Prospective blinded Evaluation of the smartphone-based AliveCor Kardia ECG monitor for Atrial Fibrillation detection: The PEAK-AF study	Prospective blinded Clinical trial	Single time point	
Raising awareness and early detection of atrial fibrillation, an experience resorting to mobile technology centered on informed individuals	A pseudo-longitudinal study/Cross-sectional	Single time point	
Screening for Atrial Fibrillation Using a Smartphone-Based Electrocardiogram in Korean Elderly	Feasibility study	Screening Only	
Artificial Neural Network for Atrial Fibrillation Identification in Portable Devices	Feasibility study	method development	
The impact of Negative to Positive Training Dataset Ratio on Atrial Fibrillation Classification Machine Learning Algorithms Performance	Feasibility study	Screening Only	
Population screening for atrial fibrillation by student pharmacists at health fairs	Feasibility study	Screening Only	
Large-scale implementation of a pragmatic atrial fibrillation screening program in Canadian community practice	Observational	Screening Only	
Identification of atrial fibrillation in secondary care diabetes and vascular clinics: a pilot study	Feasibility study	Screening Only	
Feasibility of Atrial Fibrillation Screening with Mobile Health Technologies at Pharmacies	Feasibility study	Screening Only	
Comparison and Combination of Single-Lead ECG and Photoplethysmography Algorithms for Wearable-Based Atrial Fibrillation Screening	Prospective blinded algorithm analysis	Single time point	
Diagnostic accuracy of handheld electrocardiogram devices in detecting atrial fibrillation in adults in a community versus hospital settings: a systematic review and meta-analysis	Systematic review	Not a clinical study	
Survey of current perspectives on consumer-available digital health devices for detecting atrial fibrillation	Feasibility study	Not the right device	
Mobile health applications for the detection of atrial fibrillation: a systematic review	Systematic review	Not a clinical study	
Role of wearable rhythm recordings in clinical decision making—The wEHRAbles project	Feasibility study	Not the right device	

Screening for Atrial Fibrillation Using a Mobile, Single-Lead Electrocardiogram in Canadian Primary Care Clinics	Feasibility study	Single time point	
Atrial fibrillation case finding in over 65 s with cardiovascular risk factors - Results of initial Scottish clinical experience	Feasibility study	Screening Only	
First real-world experience with mobile health telemonitoring in adult patients with congenital heart disease	Observational / cross-sectional	different indications than a diagnosis of AF	
Rise of the smart device ECG and what it means for the general cardiologist	Short-Review	Not a clinical study	
Searching for Atrial Fibrillation Post-stroke	White paper	Not a clinical study	
Lead-I ECG for detecting atrial fbrillation in patients with an irregular pulse using single time point testing: a systematic review and economic evaluation	Systematic review	Not a clinical study	
Developing and Sustaining a Career as a Transdisciplinary Nurse Scientist	Short-Review	Not a clinical study	
Effectiveness of a nongovernmental organization-led large-scale community atrial fibrillation screening program using the smartphone electrocardiogram	Observational cohort study	Screening only	
Accuracy of blinded clinician interpretation of single-lead smartphone electrocardiograms and a proposed clinical workflow	Research letter	Not a clinical study	
Economic Impact Evaluation Case Study: AliveCor Kardia Mobile	Case study	Economic model	
Classification of Atrial Fibrillation in Short-term ECG Recordings Using a Machine Learning Approach and Hybrid QRS Detection	Validation study	method development	
Rhythm and Quality Classification from Short ECGs Recorded Using a Mobile Device	Validation study	method development	
eHealth Tools to Provide Structured Assistance for Atrial Fibrillation Screening, Management, and Guideline-Recommended Therapy in Metropolitan General Practice: The AF-SMART Study	Feasibility study	Screening only	
Screening for atrial fibrillation during influenza vaccinations by primary care nurses using a smartphone electrocardiograph (iECG): A feasibility study	Feasibility study	Screening only	
Smartphone ECG aids real-time diagnosis of palpitations in the competitive college athlete	Case report	Not a clinical study	

Diagnosing symptomatic arrhythmia via mobile phone.	Case study	Not a clinical study	
Living with the handheld ECG	Commentary	Not a clinical study	
Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies The SEARCH-AF study	Cost-effectiveness	Screening only	
The diagnostic accuracy of smartphone applications to detect atrial fibrillation: head-to-head comparison between FibriCheck and AliveCor	Case-control study	Screening only	
A prospective randomized trial examining health care utilization in individuals using multiple smartphone-enabled biosensors	A prospective randomized trial	different indications than a diagnosis of AF	
A Growing Demand for on-demand Care. Perspectives from the AliveCor ECG usability study and the implications on future cardiovascular care models	Short-Review	Not a clinical study	
Smartwatch Algorithm for Automated Detection of Atrial Fibrillation	a prospective, nonrandomized, and adjudicator-blinded study	Single time point	
Arrhythmia symptoms with and without arrhythmias in patients monitored with transtelephonic ECG after AF-ablation	Abstract	Screening only	
COMMUNITY SCREENING FOR ATRIAL FIBRILLATION IN A CHINESE POPULATION USING A SMARTPHONE-BASED WIRELESS SINGLE-LEAD ECG	Abstract	Screening only	
Detection of atrial fibrillation in community locations using novel technology's as a method of stroke prevention in the over 65's asymptomatic population - Should it become standard practice?	Abstract	Screening only	
Diagnostic utility of real-time smartphone ECG in the initial investigation of palpitations	Abstract	Screening only	
Using smartphone-enabled technologies for detecting atrial fibrillation: Is there a difference in signal quality between ECG and PPG?	Abstract	Not a right device	
Efficacy of subclinical atrial fibrillation screening by AliveCor in patients with CHA2DS2-VASc score ≥2	Abstract	Screening only and Single time point	
HEAD-TO-HEAD COMPARISON OF A CAMERA-BASED SMARTPHONE APPLICATION CARDIO RHYTHMTM WITH ALIVECOR (R) HEART MONITOR FOR ATRIAL FIBRILLATION	Abstract	Single time point	

SCREENING IN PRIMARY HEALTHCARE SETTING			
Implementation of a mass atrial fibrillation screening program in Canadian community practice	Abstract	Screening only	
A novel transtelephonic tool for follow-up after atrial fibrillation ablation. Early results	Abstract	Not a right device	
QTC intervals can be assessed with the AliveCor heart monitor in patients on dofetilide for atrial fibrillation	Abstract	Screening only	
Atrial fibrillation screening in general practice by clinical pharmacists	Abstract	Screening only	
Wireless smart phone equipped ECG enables large scale screening in diverse populations	Abstract	Published as an original article one year later	
QTC intervals can be assessed with the AliveCor heart monitor in patients on dofetilide for atrial fibrillation	Abstract	Screening only	
QTC Intervals Can Be Monitored With the AliveCor Heart Monitor in Patients on Dofetilide for Atrial Fibrillation	Abstract	Screening only	
An RCT to determine if screening for atrial fibrillation reduces stroke and mortality: safer trial-screening for atrial fibrillation with ECG to reduce stroke	Abstract	Screening only	
Smartwatch Based Arrhythmia Detection: Accuracy of Clinician Interpretation of Unclassified Tracings	Abstract	Single time point	
Rationale and design of the randomized controlled trial of intensive versus usual ECG screening for atrial fibrillation in elderly Chinese by an automated ECG system in the community health center in Shanghai (AF-CATCH)	Abstract	Study protocol	
Determining Pharmacists' Ability to detect Atrial Fibrillation by utilising Mobile Single-Lead Electrocardiogram Systems (AliveCor/Kardia) in "Know Your Pulse" Awareness Campaigns	Abstract	Screening only	
A pragmatic trial integrating routine screening for atrial fibrillation in older patients during primary care visits: Initial enrolment data from the VITAL-AF trial	Abstract	Study design and protocol	
Increased yield for repeated handheld ECG screening at 6–12-month intervals to detect atrial fibrillation during outpatient clinic reviews	Abstract	Screening only	
The safer study (screening for atrial fibrillation with ECG to reduce stroke): Is it feasible to screen for atrial fibrillation in general practice	Abstract	Screening only	

Using Innovative Technology to Identify Postoperative Atrial Fibrillation in cardiac surgical patients after hospital discharge (iTIP)	Abstract	Screening only	
High prevalence but poor awareness and knowledge of atrial fibrillation among the elderly in Hong Kong	Abstract	Screening only	
Novel use of CHA2DS2VASC score to select patients to undergo repeat atrial fibrillation screening	Abstract	Screening only	
Feasibility and acceptability of atrial fibrillation screening using a hand-held ECG device in the general practice setting in Hong Kong	Abstract	Screening only	
KardiaMobile for ECG Monitoring and Arrhythmia Diagnosis	Abstract/Short review	Not a clinical study	
Accurate detection and quantification of a-trial fibrillation using a smart-watch with ECG watch band	Abstract	Single time point	
SMARTPHONE WIRELESS EKG CLOUD-BASED MANAGEMENT SYSTEM: FIRST REAL WORLD OUTPATIENT CARDIOLOGY EXPERIENCE	Abstract	Screening only	
Performance of a Mobile Single-Lead Electrocardiogram Technology for Atrial Fibrillation Screening in a Semi-Rural African Population: Insights from the Australian Led TEFF-AF Study	Abstract	Screening only	
VALIDITY OF THE ALIVECOR SOFTWARE IN DETECTING PAROXYSMAL ATRIAL FIBRILLATION: A SUB STUDY OF THE INTERMITTENT VS CONTINUOUS ANTICOAGULATION THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION (ICARE-AF) PILOT STUDY	Abstract	Algorithm validity and single time point	
Clinical Validation of a Smartphone-Based, 6-lead ECG Device	Abstract	Single time point	
Economic Impact Evaluation Case Study: AliveCor Kardia Mobile	Abstract	Economic model	
Smartphone electrocardiographic monitoring for atrial fibrillation in acute ischemic stroke and transient ischemic attack.	Abstract	Study design / protocol	
Validation of an iPhone ECG application suitable for community screening for silent atrial fibrillation: A novel way to prevent stroke	Abstract	Single time point	
Better Outcomes for Anticoagulation Treatment Through Observation of Atrial Rhythm	Observational cohort	Terminated clinical trial	

iPhone Helping Evaluate Atrial Fibrillation Rhythm Through Technology	RCT	Terminated clinical trial	
Kardia - A Smartphone-based Care Model for Outpatient Cardiac Rehabilitation	RCT	Terminated clinical trial	
Screening Education And Recognition by primary Care pHysician of Atrial Fibrillation for prevention of stroke (SEARCH-AF II)	RCT	The completion date of 2020 or below	
Screening for atrial fibrillation with ECG to reduce stroke	RCT	Not a right device	
Screening for Atrial Fibrillation With Prolonged Continuous Single-lead ECG Devices in High-risk Patients	RCT	Not a right device	
Computer Simulated Atrial Fibrillation Tool	RCT	Terminated clinical trial	
Using innovative technology to identify postoperative atrial fibrillation recurrence in non-cardiac surgical patients after hospital discharge	RCT	Terminated clinical trial	
Systematic NT-proBNP and ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm, Sweden - STROKESTOP II	RCT	Not a right device	
Validation of a Smartphone-based Recorder for Detection of Cardiac Arrhythmias	RCT	Terminated clinical trial	
Detraining on Atrial Fibrillation (DAF)	RCT	Terminated clinical trial	
Renal Nerve Denervation After Pulmonary Vein Isolation for Persistent Atrial Fibrillation	RCT	Terminated clinical trial	
Implementing Digital Health in a Learning Health System (ASE-INNOVATE)	RCT	Terminated clinical trial	
Atrial Fibrillation Research In CATalonia (AFRICAT)	RCT	Terminated clinical trial	
Atrial Fibrillation Trial to Evade Recurrence: effectS of Hiit Before electrO-Cardioversion for 3-weeKs	RCT	Terminated clinical trial	
Detection of Atrial Fibrillation in the Hospital Setting by Use of a Handheld ECG Recording Device	RCT	Terminated clinical trial	
Secondary Prevention of Atrial Fibrillation	RCT	Terminated clinical trial	
Use of AliveCor ECG Monitoring to Replicate ECG Lead Recording	RCT	Terminated clinical trial	
Feasibility and outcomes of atrial fibrillation screening using intermittent electrocardiography in a primary healthcare setting: A cross-sectional study	Cross-sectional study	Not a right device	

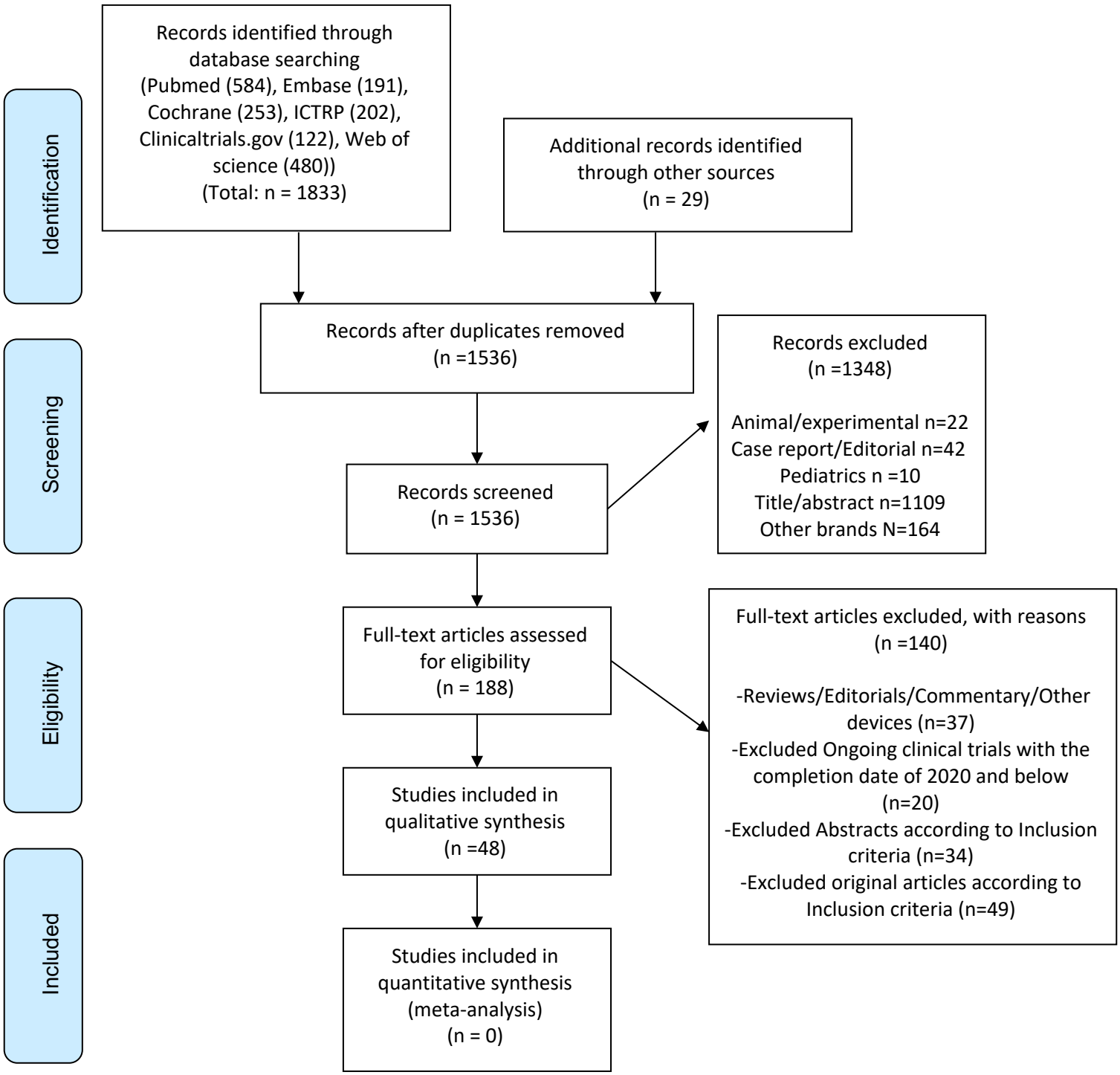
Handheld ECG Tracking of In-hOspital Atrial Fibrillation	RCT	Not a right device	
Cost-Effectiveness of Extended and One-Time Screening Versus No Screening for Non-Valvular Atrial Fibrillation in the USA	Cost-effectiveness study	Not a right device	
Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias	Observational cross-sectional study	Not a right device	
Intermittent vs continuous electrocardiogram event recording for detection of atrial fibrillation-Compliance and ease of use in an ambulatory elderly population	A sun-study of RCT	Not a right device	
Real-time smart monitoring system for atrial fibrillation pathology	Observational case-control study	Not a right device	
Screening for arrhythmia with the new portable single-lead electrocardiographic device (SnapECG): an application study in a community-based elderly population in Nanjing, China	A cross-sectional community-based study	Not a right device	
Smartphone ECG Monitoring System Helps Lower Emergency Room and Clinic Visits in Post-Atrial Fibrillation Ablation Patients	Observational case-control study	Not a right device	
Assessment of Heart Rhythm Disorders Using the AliveCor Heart Monitor: Beyond the Detection of Atrial Fibrillation	Letter	Not a clinical study	
Rise of the smart device ECG and what it means for the general cardiologist	Editorial	Not a clinical study	
Head-to-Head Comparison of the AliveCor Heart Monitor and Microlife WatchBP Office AFIB for Atrial Fibrillation Screening in a Primary Care Setting	Letter	Not a clinical study	
Time to use mobile health devices to diagnose paroxysmal atrial fibrillation	Editorial	Not a clinical study	
Comment on "Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: The REHEARSE-AF Study"	Commentary	Not a clinical study	
A single-center randomized, controlled trial investigating the efficacy of a mHealth ECG technology intervention to improve the detection of atrial fibrillation: the iHEART study protocol	Study protocol;	Not a clinical study	
Screening Education And Recognition in Community pHarmacies of Atrial Fibrillation to prevent stroke in an ambulant population aged >= 65 years (SEARCH-AF stroke prevention study): a cross-sectional study protocol	Study protocol;	Not a clinical study	

Rationale and design of the Atrial Fibrillation health Literacy Information Technology Trial: (AF-LITT)	Study protocol;	Not a clinical study	
Multi-centre randomised controlled trial of a smartphone-based event recorder alongside standard care versus standard care for patients presenting to the Emergency Department with palpitations and pre-syncope - the IPED (Investigation of Palpitations in the ED) study: study protocol for a randomised controlled trial	Study protocol;	Not a clinical study	
Atrial Fibrillation Screen, Management And Guideline Recommended Therapy (AF SMART): Implementation in the rural primary care setting	Study protocol;	Not a clinical study	
Identification of new-onset atrial fibrillation after cardiac surgery in Vietnam. A feasibility study of a novel screening strategy in a limited-resource setting: study protocol	Study protocol;	Not a clinical study	
Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection (MOBILE-AF): study protocol for a randomised controlled trial	Study protocol;	Not a clinical study	
Identification of undiagnosed atrial fibrillation patients using a machine learning risk prediction algorithm and diagnostic testing (PULsE-AI): Study protocol for a randomised controlled trial	Study protocol;	Not a clinical study	
Design and rationale of a pragmatic trial integrating routine screening for atrial fibrillation at primary care visits: the VITAL-AF trial	Study protocol;	Not a clinical study	
Screening for Atrial FibrillationWith Electrocardiography Evidence Report and Systematic Review for the US Preventive Services Task Force	Systematic review / Review	Not a clinical study	
Apple Watch, Wearables, and Heart Rhythm: where do we stand?	Systematic review / Review	Not a clinical study	
Atrial fibrillation detection using single lead portable electrocardiographic monitoring: a systematic review and meta-analysis	Systematic review / Review	Not a clinical study	
Clinical Implications of Technological Advances in Screening for Atrial Fibrillation	Systematic review / Review	Not a clinical study	
Diagnostic accuracy of handheld electrocardiogram devices in detecting atrial fibrillation in adults in community versus hospital settings: a systematic review and meta-analysis	Systematic review / Review	Not a clinical study	

Diagnostic accuracy of smart gadgets/wearable devices in detecting atrial fibrillation: A systematic review and meta-analysis	Systematic review / Review	Not a clinical study	
Effectiveness of a single lead AliveCor electrocardiogram application for the screening of atrial fibrillation A systematic review	Systematic review / Review	Not a clinical study	
Smartphone-based arrhythmia detection: Should we encourage patients to use the ECG in their pocket?	Systematic review / Review	Not a clinical study	
How useful is the smartwatch ECG?	Systematic review / Review	Not a clinical study	
Lead-I ECG for detecting atrial fibrillation in patients attending primary care with an irregular pulse using single-time point testing: A systematic review and economic evaluation	Systematic review / Review	Not a clinical study	
Mobile health applications for the detection of atrial fibrillation: a systematic review	Systematic review / Review	Not a clinical study	
Portable out-of-hospital electrocardiography: A review of current technologies	Systematic review / Review	Not a clinical study	
Role of Outpatient Cardiac Rhythm Monitoring in Cryptogenic Stroke: A Systematic Review and Meta-Analysis	Systematic review / Review	Not a clinical study	
Smart devices for a smart detection of atrial fibrillation	Systematic review / Review	Not a clinical study	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

PRISMA Flow Diagram, KardiaMobile SR



Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	11th March 2021
Date span of search:	Please see section 6
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Please see section 6	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Please see section 6.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
NA	NA	NA	NA
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE.
- all confidential sections in the submission have been marked correctly.
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included, then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*	DocuSigned by: Sean Warren B3A5E98B1C2A480...	**Date:**	Click or tap here to enter text. 4/15/2021 | 2:19 AM PDT
Print:	Sean warren Click or tap here to enter text.	**Role / organisation:**	Click or tap here to enter text. Business Director UK&I
Contact email:	Click or tap here to enter text. sean.warren@alivecor.com		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT551 KardiaMobile for the ambulatory detection of atrial fibrillation

Company evidence submission

Part 2: Economic evidence

Company name	AliveCor®
Submission date	28/04/2021
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		21 (Following de-duplication of identified studies and title and abstract screening)
Number of studies identified as being relevant to the decision problem.		5 (Following removal of studies not relevant after full-text screening)
Of the relevant studies identified:	Number of published studies.	4
	Number of abstracts.	1
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Improving Care for Patients with Atrial Fibrillation through the use of a Personal Electrocardiogram	Praus et al, 2020 (1) Location: USA	Adult patients who (1) had two or more atrial fibrillation (AF)-related emergency department (ED) or urgent care (UC) visits in the past 12 months, (2) needed rate control with medication titration, or (3) needed monitoring for AF reoccurrence after re-establishing sinus rhythm—either by chemical or direct current cardioversion.	Intervention: Providing patients with a personal single-lead electrocardiogram (the AliveCor KardiaMobile (KM) device) and telehealth access to improve AF-related outcomes. Comparator: Current practice, i.e., no use of KM device and telehealth access.	Study states that the device cost averaged $99 in 2019.	A total of 1,501 ECG recordings were received and reviewed by the end of eight weeks. Results of the KM device instant rhythm analysis revealed that 710 recordings were interpreted as normal sinus rhythm and 537 were interpreted as possible AF; of these, 74 had rapid ventricular rates. There were 173 unclassified interpretations, 46 bradycardic, 24 tachycardic, 8 deemed uncategorized (due to artifact), and 3 recordings were too short to be interpreted. Unclassified readings occur when the rhythm cannot be categorized as normal, possible AF, bradycardia, or tachycardia. Of those designated as “unclassified,” the majority came from two patients. The patient experience and satisfaction surveys were completed by 33 patients (response rate of 77%). The majority of patients gave top ratings for the program’s ability to decrease anxiety level (62% rated 5), provide empowerment to manage	The KM device, monitored by a nurse practitioner (NP), is a convenient and cost-effective example of a technology that enables more proactive and higher-quality patient care. Patients’ data can be measured at any time, and from anywhere, with the use of a smartphone; moreover, the component of the provider’s immediate intervention plays a critical role. More proactive and immediate feedback to patients when they were experiencing abnormal rhythms not only avoided costly resource utilization, but also reduced psychological burden for the patient. Patients also felt empowered to manage their AF and were less anxious about their condition. No sensitivity analyses to report.

					health concerns (72% rated 5), and increase ability to communicate with a provider and health care team (84% rated 5). Ratings were on a Likert-scale, with “1” representing that the program did not meet the question objective and “5” representing that the program did meet the question objective. When considering the ratings as scores, the overall average was 4.4 for the ability of the program to decrease anxiety level, 4.6 for being empowered to manage health concerns, and 4.8 for increased ability to communicate with a provider and health care team. Respondents were highly satisfied with 90% of them giving a rating of 5 when asked how likely they were to recommend the KM device to other patients diagnosed with AF. The survey also asked three yes/no questions. Almost all respondents (97%) found value in the additional services and the device. Virtually, all respondents (97%) also felt that the program improved their ability to directly access their	

					provider, and the majority of the respondents (87%) also felt that the program reduced unnecessary ED visits. In addition to the yes/no question regarding unnecessary ED visits, the questionnaire asked what respondents would have done if the program were not available to them; this question provided more detailed insight into patient-reported reductions in utilization. Had the respondents not been in the program, 34% (n = 11) reported that they would have presented to an ED, and 25% (n = 8) would have presented to an UC facility. The actual number of avoided resource utilization was higher than the patient responses to the survey; however, if considering 11 patients who avoided an ED visit, this quality-improvement project realized a cost savings of $81,950, using the calculated average for an ED visit. This is significantly underestimated because potential hospitalizations	

					and diverted UC visits are not included.	
Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study	Halcox et al, 2017 (2) Location: UK	Individuals >65 years of age with a CHADS-VASc score ≥2 not in receipt of oral anticoagulant (OAC) therapy without a known diagnosis of AF currently, a known contraindication to anticoagulation, or permanent cardiac pacing implantation were recruited.	Intervention: Twice-weekly monitoring with the AliveCor KM device. Participants in the intervention iECG arm were instructed to undertake twice-weekly recording and transmission of a 30-second single-lead iECG trace to a secure server (Monday and Wednesday recommended, plus additional submissions if symptomatic) over a 12-month period. Comparator: Routine care (RC).	Overall cost of the intervention provided, rather than individual unit costs. See results section for cost results.	The participants in the iECG arm recorded 60,440 ECGs over the 12-month follow-up period. Seventy-four percent of participants completed the trial without missing a single week of submission of the ECG. Recommended twice-weekly ECGs were submitted successfully on average by the iECG participants in 39 of the 52 weeks, and at least 1 weekly ECG was submitted in 48 of the 52 weeks of the trial. Of the 76% of iECGs that were reported normal by the automated algorithm, none were finally confirmed to be AF; only 6 iECGs of the 21% reported as undetermined were finally confirmed to be AF; only 5% of the ≈1% iECGs reported as AF by the device were finally confirmed to be AF; and 2.2% of iECGs were reported as unreadable. Nineteen patients in the iECG group were diagnosed with AF during the 12-month study period versus 5 in the RC arm (hazard ratio, 3.9;	This study found that regular twice-weekly iECG recording and submission is logistically feasible over a 1-year period and highly acceptable to people >65 years of age with increased risk of AF and stroke. This approach results in an almost 4-fold increase in the likelihood of a diagnosis of AF being made over the course of a year at a cost of $10,780 (£8,255) per additional AF diagnosis. The overall incidence of stroke plus TIA was similar in both groups; however, this study was not statistically powered to detect a difference in clinical events in this population. No sensitivity analyses to report.

					95% 95% confidence interval (CI)=1.4–10.4; P=0.007). Ten iECG patients had a ventricular rate >100 bpm at the time of diagnosis, and the other 9 had rates between 60 and 100 bpm. There were no significant differences in compliance between those diagnosed with AF (iECG group, n = 19) and those not diagnosed with AF (mean study weeks with iECG submitted on 2 separate days in those diagnosed versus not diagnosed with AF, 69% versus 76%, respectively; 1-way ANOVA; P=0.11). There were no significant differences in the number of serious adverse clinical events occurring in each arm. Although numerically fewer, there was no statistically significant difference in the number of strokes or transient ischemic attacks (TIAs; 6 versus 10 in the iECG and RC arms, respectively; hazard ratio=0.61; 95% CI=0.22–1.69; P=0.34). There were no peripheral arterial embolic events.	

					Participants' experience (reported with a 1–10 visual analog scale) showed small increases in the iECG arm in the reported awareness of the risk (mean score, 6.8 versus 6.1; P=0.001) but slightly less anxiety about the risk of heart rhythm abnormalities and stroke (mean score, 2.2 versus 2.5; P=0.003) and slightly lower reported likelihood of intending to visit their physician regarding concerns about their heart rhythm (mean score, 7.1 versus 7.5; P=0.04). Notably, RC participants reported a considerably greater preference to have been able to switch to the other study arm (mean score, 1.9 versus 6.2; P<0.0001). Participants in the iECG group were further asked about their experience with the AliveCor device during the study (measured on a 5-point Likert scale). The vast majority of iECG participants were not at all or slightly anxious about using the device; not at all restricted by the device; extremely or very confident using the device; extremely or very	

					comfortable with the process of sharing clinical, iECG, and personal information with the study team; and generally extremely or very satisfied with use of the device. The overall cost of the intervention was $204,830 (£156,837). This consisted of device costs of $28,698 (£21,974), patient training costs of $3,750 (£2,871), and defective technology costs of $2,194 (£1,680). A total of 60,440 ECGs were recorded, which amounted to a cost of $116,823 (£89,451) in commercial overheads of the ECG. The cost of pathway coordination of the ECGs was $37,793 (£28,938), and 704 ECGs were identified as AF by AliveCor, producing a cost of $7,972 (£6,104) for cardiologist overread. In addition, 74 review appointments were made: 44 were nurse reviews and 30 were cardiologist reviews. Overall, 19 cases of AF were detected; thus, the intervention cost was $10,780 (£8,255) per AF diagnosis.	
Economic Impact Evaluation Case	York Health Economics	Patients with a suspected	Intervention: Use of AliveCor KM in the	Unit costs included in intervention arm: AliveCor	A simple return on investment calculation was	The following scenarios were tested in sensitivity

Study: AliveCor Kardia Mobile	Consortium, 2018 (3) Location: UK	arrhythmia, such as atrial fibrillation, in a primary care setting.	diagnostic pathway for the purpose of diagnosing AF. Comparator: The 'typical' diagnostic pathway for AF. This involves two GP appointments, a 24-hour ECG, referral and follow-up out-patient cardiology appointments in secondary care and two 7-day ECG tests(s). The number of appointments and tests varied in the sensitivity analysis.	KM, including VAT = £99 (expected life of 5 years); GP appointment x 2 at £36 each = £72. Unit costs included in comparator arm: GP appointment x 2 at £36 each = £72; First cardiology outpatient appointment x 1 = £230; Follow-up cardiology appointment x 2 at £148 each = £296; ECG diagnostic = £52; 24-hour ECG = £163; 7-day ECG x 2 at £163 each = £326.	performed, based on the input costs of using the KM pathway and the value of the benefits accrued by not using the 'typical AF diagnostic pathway'. The financial impact of KM per patient being investigated for suspected AF is as follows: Cost of the KM pathway per patient investigated for AF = £171, Total value of the outcome metrics per patient investigated for AF = £1,139, Financial impact: net benefit/(deficit) per patient = £968, Return on investment in Year 1 = 666%. The analysis shows KM to give a positive return on investment and be cost saving on a per patient basis from an NHS perspective, based on the pathway described and the assumptions made. The use of KM in a typical Clinical Commissioning Group area therefore has	analysis to observe the effect on the financial impact and return on investment: • Number of patients per year: if the number of patients following the KM pathway rather than the typical AF diagnostic pathway was 100 per year, the value of savings would be £96,800 per year, and £484,000 over five years; • Number of patients per device: if one device was used in a GP consulting room, with 100 patients in a year (approximately twice a week), the cost reduces to £1 per patient and the ROI would be 1,560%, generating a net benefit of £106,601 per year; • Number of diagnostic tests in the typical pathway: if the number of 7-day ECGs tests and associated cardiology out-patient appointments is reduced to one each, the ROI decreases to 484%; • Proportion of patients in the typical pathway requiring all the tests described: if only 50% of the patients in a typical AF diagnostic pathway require all of the tests described in

					the potential to achieve savings, if implemented at scale, by avoiding diagnostics and referrals to secondary care. For example, if 250 patients per year follow the Kardia pathway rather than the 'typical AF diagnostic pathway', the value of the savings would be £242,000 per year, rising to approximately £1,210,000 over a period of five years.	the Kardia economic case, the ROI reduces to 333% and the net benefit per patient in the Kardia pathway reduces to £399. The analysis undertaken concludes that KM is a cost saving innovation, showing an estimated net benefit of £968 per patient investigated and potential ROI from an NHS perspective of 666%, based on the assumptions stated. There are also intangible patient benefits of reduced anxiety and the potential for avoided cardiovascular events, which have not been costed in this analysis.
Multi-centre Randomised Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED	Reed et al, 2019 (4) Location: UK	Patients aged 16 and over presenting to the ED with palpitations and pre-syncope with no obvious cause evident at initial consultation.	Intervention: AliveCor's KM device for the recording of events in addition to standard care. Comparator: Standard care.	Scope of the economic analysis utilised costs from primary/secondary/community care settings, as well as the cost of the intervention itself. However, no unit costs were reported in the study (only results of the economic analysis).	A symptomatic rhythm was detected at 90 days in 69 (n = 124; 55.6%; 95% CI 46.9–64.4%) participants in the intervention group versus 11 (n=116; 9.5%; 95% CI 4.2–14.8) in the control group (RR 5.9, 95% CI 3.3–10.5; p b 0.0001). A symptomatic cardiac arrhythmia was detected at 90 days in 11 (n = 124; 8.9%; 95% CI 3.9–13.9%) participants in the intervention group versus 1 (n=116; 0.9%; 95% CI 0.0–2.5%) in the control group	Use of a smartphone-based event recorder increases the symptom-rhythm correlation rate over five-fold at 90 days with a reduced cost per diagnosis. Findings suggest that a smartphone-based event recorder should be considered as part of on-going care of all patients presenting acutely with these symptoms. No sensitivity analyses to report.

(Investigation of Palpitations in the ED) Study					(RR 10.3, 95% CI 1.3–78.5; p = 0.006). The mean time to symptomatic rhythm detection in the intervention group was 9.5 days (SD 16.1, range 0–83) versus 42.9 days (SD 16.0, range 12–66) in the standard care group (p b 0.0001). The mean time to symptomatic cardiac arrhythmia detection in the intervention group was 9.9 days (SD 15.6, range 1–55) versus 48.0 days (1 participant) in the control group (p=0.0004). Eighty of 92 (87.0%) participants found the AliveCor monitor easy to use. There were more ED presentations (after index visit) due to palpitations/pre-syncope in the intervention group (12/124; 9.7%; 95% CI 4.5–14.9% with 1 or more non index ED presentations) compared to the control group (3/116; 2.6%; 95% CI 0.0–5.5%; p = 0.031). There was no difference in the number of participants with one or more inpatient hospital days (over all admissions) due to palpitations or pre-syncope in the intervention group (2; n = 122; 2 patients with no	

					data; 1.6%; 95% CI 0.0–3.8%) compared to the control group (1; n = 116; 0.9%; 95% CI 0.0–2.5%; p N 0.999), number of outpatient presentations due to palpitations or pre-syncope (p = 0.058), number of GP presentations due to palpitations or pre-syncope (p= 0.312) or number of ECGs performed due to palpitations or pre-syncope (p = 0.143). Median overall healthcare utilisation cost (primary/community/ secondary care and intervention costs) in the intervention group was £108 (IQR 99.0–246.50, range 99–2697) versus £0 in the standard care group (IQR 0–120.0, range 0–4161; p = 0.0001). Cost per symptomatic rhythm diagnosis was £921 less per patient per symptomatic rhythm in the intervention group (£474) compared to the control group (£1395).	
Comparing a Mobile ECG Device with Holter Monitoring for Patients with Palpitations in an Urgent Care	Goel et al, 2018 (5) Location: USA	Patients seeking care at urgent care centres.	Intervention: AliveCor's KM device for 30 days.	Cost of KM reported at $99 per device.	The KM device was diagnostically superior to, or concordant with, Holter monitoring in 82.0% of patients. Holter monitoring was superior in 16.0% of patients. Arrhythmias	At $99, the KM is a cost-efficient device that can be used to screen urgent care patients with palpitations. In most patients, it determines

Setting: A Preliminary Study			Comparator: 24-hour Holter monitoring.		detected included atrial and ventricular ectopy, SVT and VT, atrial fibrillation and inappropriate sinus tachycardia.	whether further cardiac investigation is required.
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Improving Care for Patients with Atrial Fibrillation through the use of a Personal Electrocardiogram Praus et al, 2020 (1)	
What are main differences in resource use and clinical outcomes between the technologies?	The patient experience and satisfaction surveys completed by patients receiving the intervention indicated high levels of satisfaction with the KM device: The majority of patients gave top ratings for the program's ability to decrease anxiety level (62% rated 5), provide empowerment to manage health concerns (72% rated 5), and increase ability to communicate with a provider and health care team (84% rated 5). The survey also asked three yes/no questions. Almost all respondents (97%) found value in the additional services and the device. Virtually, all respondents (97%) also felt that the program improved their ability to directly access their provider, and the majority of the respondents (87%) also felt that the program reduced unnecessary ED visits. In addition to the yes/no question regarding unnecessary ED visits, the questionnaire asked what respondents would have done if the program were not available to them; this question provided more detailed insight into patient-reported reductions in utilization. Had the respondents not been in the program, 34% (n = 11) reported that they would have presented to an ED, and 25% (n = 8) would have presented to an UC facility. If considering 11 patients who avoided an ED visit, this quality-improvement project realized a cost savings of $81,950, using the calculated average for an ED visit. This is significantly underestimated because potential hospitalizations and diverted UC visits are not included.

How are the findings relevant to the decision problem?	Based on the results presented, introduction of the KM device has the potential to improve patient's experience and quality-of-life, whilst resulting in cost savings for the health care system due to the avoidance of unnecessary hospital visits.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Claimed benefits of the technology which are supported in this publication include: • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Little if any preparation is required for patients using the device so ECG recordings are simple, painless, and do not impact QOL. • Avoiding unnecessary referral to secondary care could lead to cost savings. • Ease of implementation; minimal changes in facilities or infrastructure needed when KardiaMobile is adopted in standard practice, including in rural areas.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Questionnaire administered to patients asked whether the patient would have presented to the ED had they not been involved in the program. Based on the number of respondents indicating that they would have presented, the total cost saving associated with the avoidance of unnecessary ED visits was estimated: Quality-improvement project realized a cost savings of $81,950. The authors stress that this may be an underestimate of total cost savings due to the fact that the avoidance of unnecessary UC visits, and other hospitalizations, was not included in this total.
What are the limitations of this evidence?	• The project involved a single, cardiology practice and may not be representative of patients in other practices or geographic locations. • Statistical testing could not be conducted given the small number of participants.

	• The KM device has the potential for long-term monitoring; thus, a project with longer follow-up would be needed to examine the use of KM beyond eight weeks. • 4 of the 43 participants had already been using their own KM device prior to enrolment; therefore, they may have already experienced a reduction in anxiety levels through their use and comfort with the device prior to the project period. • Utilization reductions were based on patient self-report and did include clinical review of the episodes to document the clinical pathway of the patient; moreover, patient recall could be an issue with completion of the survey at the end of the project period. • Finally, there are many uses of the KM device that were not included, such as screening high-risk patients for AF, investigation of symptomatic patients (e.g., palpitations) for AF, and the like. Future projects should explore more of the potential uses for KM.
How was the study funded?	Funding obtained from Southwest Medical, part of OptumCare for the Kardia-Mobile devices.

Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study Halcox et al, 2017 (2)	
What are main differences in resource use and clinical outcomes between the technologies?	There were no significant differences in the number of serious adverse clinical events occurring in each arm. Although numerically fewer, there was no statistically significant difference in the number of strokes or transient ischemic attacks (TIAs; 6 versus 10 in the iECG and RC arms, respectively; hazard ratio=0.61; 95% CI=0.22–1.69; P=0.34). Participants' experience (reported with a 1–10 visual analog scale) showed small increases in the iECG arm in the reported awareness of the risk (mean score, 6.8 versus 6.1; P=0.001) but slightly less

	anxiety about the risk of heart rhythm abnormalities and stroke (mean score, 2.2 versus 2.5; P=0.003) and slightly lower reported likelihood of intending to visit their physician regarding concerns about their heart rhythm (mean score, 7.1 versus 7.5; P=0.04). Notably, routine clinical care participants reported a considerably greater preference to have been able to switch to the other study arm (mean score, 1.9 versus 6.2; P<0.0001). Participants in the iECG group were asked about their experience with the AliveCor device during the study (measured on a 5-point Likert scale). The vast majority of iECG participants were not at all or slightly anxious about using the device; not at all restricted by the device; extremely or very confident using the device; extremely or very comfortable with the process of sharing clinical, iECG, and personal information with the study team; and generally extremely or very satisfied with use of the device. Costs associated with use of the technology, as well as cost per AF diagnosis were estimated. The overall cost of the intervention was $204,830 (£156,837), while the intervention cost was $10,780 (£8,255) per AF diagnosis.
How are the findings relevant to the decision problem?	Based on the results presented, introduction of the KM device has the potential to improve patient experience and reduce anxiety. Additionally, confidence in use of the device appears very high among participants. Finally, the study finds that the cost per diagnosis of AF to be $10,780 (£8,255) according to current National Health Service tariffs.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Claimed benefits of the technology which are supported in this publication include: • Ease of use with minimal disruption to patients' daily activities leading to improved patient compliance and data collection. • Little if any preparation is required for patients using the device so ECG recordings are simple, painless, and do not impact QOL. • Ease of implementation; minimal changes in facilities or infrastructure needed when

	KardiaMobile is adopted in standard practice, including in rural areas.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	The costs associated with screening for AF with the AliveCor device were estimated from the perspective of the National Health Service and Personal Social Services using data from study activity and relevant costs. The overall cost of the intervention was $204,830 (£156,837). This consisted of device costs of $28,698 (£21,974), patient training costs of $3,750 (£2,871), and defective technology costs of $2,194 (£1,680). A total of 60,440 ECGs were recorded, which amounted to a cost of $116,823 (£89,451) in commercial overreads of the ECG. The cost of pathway coordination of the ECGs was $37,793 (£28,938), and 704 ECGs were identified as AF by AliveCor, producing a cost of $7,972 (£6,104) for cardiologist overread. In addition, 74 review appointments were made: 44 were nurse reviews and 30 were cardiologist reviews. Overall, 19 cases of AF were detected; thus, the intervention cost was $10,780 (£8,255) per AF diagnosis.
What are the limitations of this evidence?	• Patients who did not have access to the Internet or could not use the device were excluded from participation in the study, excluding those who could not comply with the monitoring protocol, likely including a proportion of those at highest risk. This introduces a potential selection bias toward our findings being representative of this approach in the more independent, educated elderly who would likely still benefit considerably from lower AF-related stroke risk. • Despite their generally very good concordance with the monitoring protocol and higher AF diagnosis rate, it is likely that asymptomatic paroxysmal AF was missed in some participants, although it is unlikely that persistent/permanent AF was missed.

	• Only the iECG patients were contacted and brought back for clinical review with or without further testing when clinically indicated by their iECG results. There was no specific instruction for how to manage routine clinical care patients, and data on the nature and frequency of these visits for comparison have not been formally evaluated. • The authors did not complete a full assessment of the diagnostic performance of the device and the reporting service. This is an extensive undertaking and was beyond the scope of this study. • The study was not blinded, with electrocardiographic overreads, diagnosis of AF, and determination of clinical outcomes undertaken by the senior physician investigators. Although electrocardiographic and clinical diagnoses were validated, an element of observer bias cannot be excluded. • The study was conducted in a single centre based in a UK University Hospital with the majority of participants of white European ethnicity; thus, the findings may not be generalizable to different patient populations or healthcare systems.
How was the study funded?	The study was funded by a joint grant from the Welsh Government Health Technology and Telehealth Fund and AliveCor Inc.

Economic Impact Evaluation Case Study: AliveCor Kardia Mobile York Health Economics Consortium, 2018 (3)	
What are main differences in resource use and clinical outcomes between the technologies?	A simple return on investment calculation was performed, based on the input costs of using the Kardia Mobile pathway and the value of the benefits accrued by not using the 'typical AF diagnostic pathway'.

	The financial impact of Kardia Mobile per patient being investigated for suspected AF is as follows: Cost of the Kardia Mobile pathway per patient investigated for AF = £171, Total value of the outcome metrics per patient investigated for AF = £1,139, Financial impact: net benefit/(deficit) per patient = £968, Return on investment in Year 1 = 666%. The analysis shows KM to give a positive return on investment and to be cost saving on a per patient basis from an NHS perspective, based on the pathway described and the assumptions stated.
How are the findings relevant to the decision problem?	The findings indicate that the introduction of KM into the pathway of diagnosis of AF could potentially lead to cost savings for the NHS. By avoiding current diagnostics and referrals to secondary care, significant cost savings could potentially be made if implemented at scale.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Claimed benefits of the technology which are supported in this publication include: • Avoiding unnecessary referral to secondary care could lead to cost savings. • Reduction in health service resource use such as staff in the ambulatory ECG monitoring pathway, due to reduce the in-clinic analysis of ECG recordings and reduced outpatient appointments.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Study examined the existing cost of the diagnostic pathway for AF in the English healthcare system, and estimated the cost savings that could potentially be made if the KM device was introduced as an alternative to this typical diagnostic pathway.

	The authors estimated a cost saving of £968 on a per patient basis, which amounts to a return on investment of 666% in the first year. The authors conclude that the use of KM in a typical Clinical Commissioning Group area therefore has the potential to achieve savings, if implemented at scale, by avoiding diagnostics and referrals to secondary care. They estimate that if 250 patients per year followed the Kardia pathway rather than the 'typical AF diagnostic pathway', the value of the savings would be £242,000 per year, rising to approximately £1,210,000 over a period of five years. The total return on investment is impacted by the assumed number of patients that would use each device, and the proportion of patients in the existing pathway that actually receive all of the diagnostics that have been costed.
What are the limitations of this evidence?	• The analysis does not include the diagnostic performance of the KM device compared to other tests in use by GPs, e.g. pulse check. There is, however, good evidence for the sensitivity and specificity of the ECG algorithm used by KM. • The information on the 'typical AF diagnostic pathway' includes assumptions and may not be typical in all locations. • The analysis does not include the value of patient benefits accrued from reduced anxiety and avoided cardiovascular events.
How was the study funded?	Not stated.

Multi-centre Randomised Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED (Investigation of Palpitations in the ED) Study Reed et al, 2019 (4)

What are main differences in resource use and clinical outcomes between the technologies?	A symptomatic rhythm was detected at 90 days in 69 (n = 124;55.6%; 95% CI 46.9–64.4%) participants in the intervention group versus 11 (n=116; 9.5%; 95% CI 4.2–14.8) in the control group (RR 5.9, 95% CI 3.3–10.5; p b 0.0001). A symptomatic cardiac arrhythmia was detected at 90 days in 11 (n = 124; 8.9%; 95% CI 3.9–13.9%) participants in the intervention group versus 1 (n=116; 0.9%; 95% CI 0.0–2.5%) in the control group (RR 10.3, 95% CI 1.3–78.5; p = 0.006). The mean time to symptomatic rhythm detection in the intervention group was 9.5 days (SD 16.1, range 0–83) versus 42.9 days (SD 16.0, range 12–66) in the standard care group (p b 0.0001). The mean time to symptomatic cardiac arrhythmia detection in the intervention group was 9.9 days (SD 15.6, range 1–55) versus 48.0 days (1 participant) in the control group (p=0.0004). Serious outcome at 90 days in the intervention group was 11 (8.9%) versus 2 (1.7%) in the control group (p= 0.02). At 90 days, 12 participants in the intervention group were subsequently undergoing (or planning to undergo) treatment for symptomatic cardiac arrhythmia versus 6 in the control group (p = 0.192). Eighty of 92 (87.0%) participants found the AliveCor monitor easy to use. There were more ED presentations (after index visit) due to palpitations/pre-syncope in the intervention group (12/124; 9.7%; 95% CI 4.5–14.9% with 1 or more non index ED presentations) compared to the control group (3/116; 2.6%; 95% CI 0.0–5.5%; p = 0.031). Median overall healthcare utilisation cost (primary/community/ secondary care and intervention costs) in the intervention group was £108 (IQR 99.0–246.50, range 99–2697) versus £0 in the standard care group (IQR 0–120.0, range 0–4161; p = 0.0001). Cost per symptomatic rhythm diagnosis was £921 less per patient per symptomatic rhythm in the intervention group (£474) compared to the control group (£1,395).

How are the findings relevant to the decision problem?	The findings indicate that the introduction of KM may increase the detection rate of cardiac arrhythmia and may do so quicker than with current practice. Additionally, findings indicate that patient satisfaction is high amongst patients utilising the technology, and the cost per symptomatic rhythm diagnosis is less on a per patient basis than with current practice (- £921).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Claimed benefits of the technology which are supported in this publication include: • KardiaMobile will lead to earlier diagnosis and initiation of treatment to control AF which could prevent the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Little if any preparation is required for patients using the device so ECG recordings are simple, painless, and do not impact QOL. • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke, or heart failure. • Avoiding unnecessary referral to secondary care could lead to cost savings
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Study estimated the median overall healthcare utilisation costs associated with the two strategies being compared, taking into account primary, secondary, and community care costs as well as the cost of the intervention. The authors also estimated the cost per symptomatic rhythm diagnosis for the two strategies being compared. Median overall healthcare utilisation cost (primary/community/secondary care and intervention costs) in the intervention group was £108 (IQR 99.0–246.50, range 99–2697) versus £0 in the standard care group (IQR 0–120.0, range 0–4161; p = 0.0001). Cost per symptomatic rhythm diagnosis was £921 less per patient per

	symptomatic rhythm in the intervention group (£474) compared to the control group (£1395).
What are the limitations of this evidence?	• A large proportion of recruitment occurred in office hours largely by research staff in research active hospitals, and the use of a central ECG reading service may not be available in routine practice.
How was the study funded?	The study was funded by Chest, Heart and Stroke Scotland (Action Research Grant R15/A164; £23,056) and British Heart Foundation (BHF Project Grant no. PG/17/63/33198; £21,347) which included funding for purchasing the devices.

Comparing a Mobile ECG Device with Holter Monitoring for Patients with Palpitations in an Urgent Care Setting: A Preliminary Study Goel et al, 2018 (5)	
What are main differences in resource use and clinical outcomes between the technologies?	The KM device was diagnostically superior to or concordant with Holter monitoring in 82.0% of patients in an urgent care setting. Holter monitoring was superior in 16.0% of patients. Arrhythmias detected included atrial and ventricular ectopy, SVT and VT, atrial fibrillation and inappropriate sinus tachycardia.
How are the findings relevant to the decision problem?	The findings of this study indicate that introduction of KM is not diagnostically inferior to existing methods for diagnosing AF, and that given the low cost of the KM device ($99) it is likely to be a cost-effective use of health care service resources.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Claimed benefits of the technology which are supported in this publication include: • Improved identification of people with AF, could lead to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke, and heart failure. • Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of

	arrhythmia, such as syncope, stroke, or heart failure.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	No cost analysis reported in this abstract. However, the authors highlight the low cost of the KM device ($99). Placing this in the context of the clinical benefits outlined, the authors hypothesise that introduction of the intervention is likely to be a cost-effective use of health service resources.
What are the limitations of this evidence?	No limitations reported in abstract.
How was the study funded?	This study was funded by AliveCor, Inc., which is the parent company and creator of the KardiaMobile device.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Adults (average starting age of 64 in the model) with known, or suspected, AF who are referred for ambulatory ECG monitoring. The patient population consist of adults, who are symptomatic, referred for ambulatory ECG monitoring in secondary care. Due to lack of data, the asymptomatic population was not included in the model.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Use of the KardiaMobile system (KardiaMobile hardware [single-lead or 6 lead ECG monitor] and KardiaMobile app) for the ambulatory detection of AF compared with (1) Holter monitoring (24h, 48h, and 7-day), and (2) use of the Zio patch electrode monitor (PEM) (14-day).

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

A Markov-cohort economic model was developed to capture the short- and long-term costs and health outcomes associated with monitoring for AF with KardiaMobile, and alternative technologies. The model consisted of two parts. The first stage of the model (which utilises a daily cycle length) considers initial AF diagnosis, while the second stage considers potential preventive treatment (use of anticoagulants or no treatment), and cardiovascular complications followed by AF or adverse events caused by anticoagulants. In the second part of the model, patients are initially classified in three health states of ‘diagnosed AF (no complications)’, ‘undiagnosed AF’, and ‘no AF’ according to the results of ambulatory electrocardiogram (AECG) monitoring in the first 100 days (first stage of the model). In the latter part of the model, patients may progress through the model pathways, based on

the occurrence of complications, over an annual cycle length. The model was developed from the perspective of the National Health Service (NHS) in England and Personal Social Services (PSS), with costs and outcomes estimated over a five-year time horizon (base-case analysis; with the model allowing for alternative durations to be explored). Costs and health outcomes occurring beyond 1 year were discounted at a rate of 3.5% (6). The model structure was partially informed by the NICE clinical guidelines on the management of AF (7), as well as related clinical and cost-effectiveness literature. The structure of the model can be seen in Appendix B.

The model describes the AF diagnostic, preventive treatment, and complication management pathways. The first part of the model captures the initial diagnosis of AF. It was developed in a Markov trace to incorporate daily age- and sex-specific mortality rates associated with various monitoring times of the different technologies. Patients in the model receive an initial diagnosis based on the particular device that they have received, i.e., intervention or comparator(s). Only KardiaMobile is able to return positive, negative, or inconclusive results, while other included technologies provide an ECG result that a clinician should interpret. Therefore, a two-step diagnostic approach consists of monitoring by the device, followed by interpretation from a clinician. Following clinical assessment, the model categorises patients as a true positive (TP) case of AF or a false positive (FP) case. A FP case would then either undergo repeat monitoring or no further follow-up in the first stage of the model. Alternatively, patients may be categorised as a true negative (TN) case of AF or a false negative (FN) case. Negative patients (both TN and FN) do not receive subsequent follow-up monitoring. Finally, initially 'inconclusive' results from the device may also undergo subsequent clinical assessment, at which point patients are categorised as AF positive or AF negative. Neither group undergo further follow-up testing, but cases that remain inconclusive following clinical assessment receive repeat monitoring.

The model uses the true prevalence rate of AF based on the CRYSTAL-AF study results (Sanna et al, 2014) (8) to estimate the undiagnosed AF percentage at the beginning of the monitoring phase. When patients used AF monitoring devices, AF positive cases were detected per day and they were moved from undiagnosed AF to diagnosed AF. Patients with diagnosed AF received, and adhered to, either anticoagulation or no treatment. In the analysis, the probabilities of true, false, and inconclusive KardiaMobile results after the clinician's decision were estimated based on information from Hermans et al, 2021 (9). For the comparators, it was assumed that the sensitivity of the monitoring technologies (Holter, CER, and Zio) was equal to the positive diagnostic yield rates. Therefore, there was no risk of FPs for the comparators in the model. Moreover, non-positive cases after Holter, CER, and Zio were not considered as AF negative. These cases were classified in the inconclusive arm, and after clinical decision they may undergo subsequent AF monitoring or move into the No AF health state. The probabilities of those who were a candidate for subsequent AF monitoring were based on different sources. For Holter monitoring, the rate of 27% was highlighted by the EAC group in the Zio supporting document based on an analysis of the HES data (10). For CER and Zio, we used the rate of 1.465 additional monitoring for undiagnosed AF cases. The diagnostic accuracy of the subsequent monitoring steps was assumed to be independent of the initial step. In the case of test-positive results, anticoagulant therapy was prescribed.

Following the diagnostic stage of the model (first stage), patients enter the second stage of the model. As outlined earlier, patients begin the model in one of three health states: (1) AF with no complications (TP and FN cases from the first component of the model), (2) No AF, and (3) Undiagnosed AF (a subset of patients for whom results of AF monitoring have not been diagnostic yield). Patients with AF with no complications undergo treatment for the condition, while patients with no AF, and with undiagnosed AF, do not receive treatment. Undetected AF (FNs) is associated with a higher risk of complications. The second part of the model captures the subsequent probabilities of patients

experiencing a number of clinical events including stroke, myocardial infarction (MI), intracranial haemmorhage (ICH), and major bleeding (MB). The probability of these events occurring is determined based on whether or not the patient has AF and the accuracy of their original diagnosis i.e., whether or not the patient is receiving treatment for their condition and the type of treatment that the patient is receiving, i.e., aspirin, warfarin, or a novel oral anticoagulant (NOAC). Patients in the model may either remain in their initial health state or, where patients experience clinical adverse events, progress to subsequent health states in the model ('Single event', 'Two events', 'Three events', 'Four events') to account for the impact that experiencing an adverse event, and multiple adverse events, would have on costs and health-related quality-of-life (HRQoL). The probability of patient's experiencing subsequent adverse events is also impacted by whether or not the patient has experienced a prior event.

Patients may also die in any cycle of the model, in which event they enter an absorbing 'Dead' health state. Simulated patients are at risk of death from all causes during any model cycle. Risk of death is conditional on whether or not the patient has AF, their clinical history in terms of events experienced, and age. The all-cause mortality rates were derived from general population mortality statistics reported in national life tables and were adjusted to reflect the extra mortality associated with their condition. In order to evaluate the face validity of the model, the model structure, input parameters and results were presented to clinical experts in the team. The experts were asked to evaluate the model structure and assumptions in comparison to real-world circumstances. A wide range of sensitivity analyses was also conducted to explore uncertainty in the model results and to assess the internal validity of the model. Null and extreme values were assigned to input parameters and the model was run to test the robustness of the outputs. The model estimated the impact of the alternative AF monitoring interventions on patient survival, as well as on long-term costs and quality-adjusted life-years (QALYs).

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
All monitoring tests with Holter, Zio or continuous event recorder (CER) would be followed-up with an outpatient clinic visit (GP or specialist), regardless of findings.	Clinical expert opinion and based on information provided in NICE MTG52 (10).	Clinical expert opinion NICE MTG52 (10)
With KardiaMobile, only patients receiving a positive result are followed-up with a visit to the GP or cardiologist. Otherwise, the clinician reaches a decision based on an interpretation of the ECG findings submitted.	Clinical expert opinion.	Clinical expert opinion
The base-case cost-effectiveness analysis considers ambulatory ECG in a secondary care setting.	Based on the NICE Scope document.	NICE Scope document
The model consists of symptomatic patients only.	The asymptomatic population will not be included in the model due to the small proportion of the population who are candidates for ambulatory ECG, and the lack of data for the asymptomatic population regarding the probability of a positive test with KardiaMobile and other comparators in the ambulatory setting.	Clinical expert opinion
In the model, negative, and confirmed positive results by the clinician will not lead to repeat ambulatory ECG.	Clinical expert opinion.	Clinical expert opinion
Where monitoring is repeated (undiagnosed AF patients), the same device (always in the case of KardiaMobile) or an alternative technology may be used (e.g., CER after Holter 24h) following the initial monitoring. The use of an implantable device is an option when there is a significant concern. The model assumes a maximum of two repeat tests, including implementable loop recorders (LRs), after the initial test.	Clinical expert opinion.	Clinical expert opinion

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Proportion male patients	NHS Hospital Episodes Statistics data (11)	0.55	0.55-0.55	Used to determine the percentage of male/female patients in the model from the outset, impacting subsequent clinical outcomes and costs.
Prevalence of AF	Sanna et al, 2014 (8)	0.30	0.23-0.38	Used to determine the prevalence of atrial fibrillation amongst patients from the outset of the model, which impacts the number of positive and negative cases of atrial fibrillation identified with the alternative methods of diagnosis.
Duration of monitoring with KardiaMobile (days)	Hermans et al, 2021 (9)	14	14-14	Used to determine the length of time over which patients would be monitored with KardiaMobile.
Duration of monitoring with Zio (days)	NICE MTG52 (10)	14	14-14	Used to determine the length of time over which patients would be monitored with Zio.
Waiting time for diagnosis with KardiaMobile (days)	Assumption	3	2-5	Used to determine the length of time patients would need to wait before receiving a diagnosis with KardiaMobile.
Waiting time for diagnosis with Holter (days)	Assumption	3	2-5	Used to determine the length of time patients would need to wait before receiving a diagnosis with Holter.
Waiting time for diagnosis with Zio (days)	Assumption	3	2-5	Used to determine the length of time patients would need to wait before receiving a diagnosis with Zio.
Maximum duration of monitoring with CER (days)	Kaura et al, 2019 (12)	30	30-30	Used to determine the length of time over which patients would be monitored with CER.
Waiting time for diagnosis with CER (days)	Assumption	3	2-5	Used to determine the length of time patients would need to wait before receiving a diagnosis with CER.

Rate of repeat monitoring after Holter	NICE MTG52 (10)	0.27	0.27-0.27	Used to determine the rate of repeat monitoring after Holter.
Rate of repeat monitoring after CER	Calculation*	0.179	0.179-0.179	Used to determine the rate of repeat monitoring after CER.
Rate of repeat monitoring after Zio	Calculation*	0.176	0.176-0.176	Used to determine the rate of repeat monitoring after Holter.
Rate of GP visits during the initial AF monitoring (base-case)	Clinical expert opinion	0.00	0.00-0.00	Used to determine the rate of GP visits when undergoing initial AF monitoring.

*Rate of repeat monitoring estimated assuming 1.465 additional monitoring (NICE MTG52 (10)) of undiagnosed cases after initial ambulatory monitoring, and with an assumed maximum of two ambulatory monitoring during the AF detection period.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

Not applicable.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	Five years (base-case analysis, with the model containing the functionality to explore alternative time horizons, including lifetime).	In order to capture all the potential clinical and cost outcomes associated with using the technology over a sufficient duration of time. Although the model is capable of exploring alternative	NICE Scope document

		time horizons, the team believes a five-year horizon is sufficient to capture all potential costs and outcomes associated with introduction of KardiaMobile, compared to alternative technologies.	
Discount rate	3.5%.	As per NICE recommendation, applied to both costs and benefits.	NICE 2013 HTA guideline (6)
Perspective (NHS/PSS)	NHS and personal social services perspective.	As specified in the final scope.	NICE Scope document
Cycle length	1 day in the first stage of the model, and 1 year in the second stage of the model.	Appropriate duration of time to reflect transition of patients in each stage of the model.	N/A
Transition probabilities	**First stage of the model:** *Primary monitoring* Probability of diagnostic yield (KardiaMobile) = 0.93 Probability of diagnostic yield (KardiaMobile + Clinician) = 0.93 Probability of diagnostic yield (Holter 24H) = 0.13 Probability of diagnostic yield (Holter 48H) = 0.14 Probability of diagnostic yield (Holter 7 days) = 0.15 Probability of diagnostic yield (Zio) = 0.16 Probability of diagnostic yield (CER) = 0.16 Probability of AF positive (KardiaMobile) = 0.36 Probability of AF positive (KardiaMobile + Clinician) = 0.36	For the first stage of the model, data related to the accuracy of the KardiaMobile device, Holter monitoring, Zio and CER were derived from a combination of previous studies and assumptions based on clinical expert input. Studies by Hermans et al, 2021 (9), which involved a direct comparison between KardiaMobile and Holter monitoring (24h, 48h and 7 days), Kaura et al, 2019 (12), and Gladstone et al, 2014 (13) were used to source this information. The probabilities of using alternative tests following each initial monitoring test were informed by expert clinical input. Data to populate the long-term Markov component of the model were sourced from a combination of assumptions	Hermans et al, 2021 (9) Kaura et al, 2019 (12) Gladstone et al, 2014 (13) Diamantopoulos et al, 2016 (14) Hill et al, 2020 (15)

	Probability of AF positive (Holter 24h) = 1.00 Probability of AF positive (Holter 48h) = 1.00 Probability of AF positive (Holter 7 days) = 1.00 Probability of AF positive (Zio) = 1.00 Probability of AF positive (CER) = 1.00 Probability of true AF positive (KardiaMobile) = 1.00 Probability of true AF positive (KardiaMobile + Clinician) = 0.77 Probability of true AF positive (Holter 24h) = 1.00 Probability of true AF positive (Holter 48h) = 1.00 Probability of true AF positive (Holter 7 days) = 1.00 Probability of true AF positive (Zio) = 1.00 Probability of true AF positive (CER) = 1.00 Probability of true AF negative (KardiaMobile) = 1.00 Probability of true AF negative (KardiaMobile + Clinician) = 1.00 Probability of true AF negative (Holter 24h) = 0.00 Probability of true AF negative (Holter 48h) = 0.00 Probability of true AF negative (Holter 7 days) = 0.00 Probability of true AF negative (Zio) = 0.00	informed by clinical expert input, and previous studies. The proportion of diagnosed AF patients receiving alternative types of treatment was informed by expert clinical input. Data on the annual risk of different types of clinical adverse events were sourced from studies by Diamantopoulos et al, 2016 (14) and Hill et al, 2020 (15). Hazard ratios related to the risk of experiencing an event on different types of treatment, and related to the risk of experiencing an event having previously suffered an event, were primarily based on data from Hill et al, 2020 (15).	

	Probability of true AF negative (CER) = 0.00 Probability of repeat monitoring after FP (KardiaMobile) = 0.00 Probability of repeat monitoring after FP (KardiaMobile + Clinician) = 0.11 Probability of repeat monitoring after FP (Holter 24h) = 0.00 Probability of repeat monitoring after FP (Holter 48h) = 0.00 Probability of repeat monitoring after FP (Holter 7 days) = 0.00 Probability of repeat monitoring after FP (Zio) = 0.00 Probability of repeat monitoring after FP (CER) = 0.00 Probability of AF positive – inconclusive (KardiaMobile) = 0.00 Probability of AF positive – inconclusive (KardiaMobile + Clinician) = 0.03 Probability of AF positive – inconclusive (Holter 24h) = 0.00 Probability of AF positive – inconclusive (Holter 48h) = 0.00 Probability of AF positive – inconclusive (Holter 7 days) = 0.00 Probability of AF positive – inconclusive (Zio) = 0.00 Probability of AF positive – inconclusive (CER) = 0.00 Probability of AF negative – inconclusive (KardiaMobile) = 1.00		

	Probability of AF negative – inconclusive (KardiaMobile + Clinician) = 0.95 Probability of AF negative – inconclusive (Holter 24h) = 0.60 Probability of AF negative – inconclusive (Holter 48h) = 0.60 Probability of AF negative – inconclusive (Holter 7 days) = 0.68 Probability of AF negative – inconclusive (Zio) = 0.00 Probability of AF negative – inconclusive (CER) = 1.00 Probability of repeat monitoring after inconclusive test (KardiaMobile) = 0.00 Probability of repeat monitoring after inconclusive test (KardiaMobile + Clinician) = 0.02 Probability of repeat monitoring after inconclusive test (Holter 24h) = 0.31 Probability of repeat monitoring after inconclusive test (Holter 48h) = 0.31 Probability of repeat monitoring after inconclusive test (Holter 7 days) = 0.32 Probability of repeat monitoring after inconclusive test (Zio) = 0.05 Probability of repeat monitoring after inconclusive test (CER) = 0.00 Probability of no AF (KardiaMobile) - inconclusive = 0.00 Probability of no AF (KardiaMobile + Clinician) - inconclusive = 0.50 Probability of no AF (Holter 24h) - inconclusive = 0.77		

	Probability of no AF (Holter 48h) - inconclusive = 0.77 Probability of no AF (Holter 7 days) - inconclusive = 0.82 Probability of no AF (Zio) – inconclusive = 0.89 Probability of no AF (CER) - inconclusive = 0.89 *Repeat monitoring pattern* First round: KardiaMobile following KardiaMobile = 1.00 Holter 7d following KardiaMobile = 0.00 CER following KardiaMobile = 0.00 KardiaMobile following Holter 24h = 0.00 Holter 7d following Holter 24h = 0.80 CER following Holter 24h = 0.10 KardiaMobile following Holter 48h = 0.00 Holter 7d following Holter 48h = 0.90 CER following Holter 48h = 0.10 KardiaMobile following Holter 7 days = 0.00 Holter 7d following Holter 7 days = 0.60 CER following Holter 7 days = 0.40 KardiaMobile following Zio = 0.00 Holter 7d following Zio = 0.00 CER following Zio = 1.00 Second round:		

	KardiaMobile following KardiaMobile = 1.00 Holter 7d following KardiaMobile = 0.00 CER following KardiaMobile = 0.00 Loop Recorder following KardiaMobile = 0.00 KardiaMobile following Holter 24h = 0.00 Holter 7d following Holter 24h = 0.00 CER following Holter 24h = 0.70 Loop Recorder following Holter 24h = 0.30 KardiaMobile following Holter 48h = 0.00 Holter 7d following Holter 48h = 0.00 CER following Holter 48h = 0.70 Loop Recorder following Holter 48h = 0.30 KardiaMobile following Holter 7 days = 0.00 Holter 7d following Holter 7 days = 0.00 CER following Holter 7 days = 0.60 Loop Recorder following Holter 7 days = 0.40 KardiaMobile following Zio = 0.00 Holter 7d following Zio = 0.00 CER following Zio = 0.60 Loop Recorder following Zio = 0.40 **Second stage of the model:** *Treatment of diagnosed patients* Proportion of patients receiving no treatment = 0.05 Proportion of patients on aspirin = 0.05		

	Proportion of patients on warfarin = 0.10 Proportion of patients on NOAC = 0.80 *Annual risk of clinical adverse events* Risk of ischemic stroke for patients without AF = 0.05 Risk of ischemic stroke for undetected AF patients = 0.08 Risk of ischemic stroke for detected AF patients = 0.03 Risk of ICH when on aspirin = 0.006 Risk of ICH when on warfarin = 0.01 Risk of ICH when on NOAC = 0.006 % of ICH that is haemorrhagic stroke = 0.6 Risk of major bleeding when on aspirin = 0.01 Risk of major bleeding when on warfarin = 0.01 Risk of major bleeding when on NOAC = 0.13 Base probability of stroke = 0.012 Base probability of major bleeding = 0.066 Base probability of MI = 0.008 Base probability of ICH = 0.009 Base probability of all-cause mortality = 0.038 *Hazard ratios* HR of experiencing major bleeding when undetected AF = 0.51 Stroke when on no treatment compared to warfarin = 3.00		

	Stroke when on NOAC compared to warfarin = 0.90 Stroke when on aspirin compared to warfarin = 1.04 Major bleeding when undetected AF = 0.51 Major bleeding when on no treatment compared to warfarin = 0.51 Major bleeding when on NOAC compared to warfarin = 0.82 Major bleeding when on aspirin compared to warfarin = 1.04 MI when on no treatment compared to warfarin = 0.51 MI when on NOAC compared to warfarin = 0.86 MI when on aspirin compared to warfarin = 1.04 ICH when on no treatment compared to warfarin = 1.65 ICH when on NOAC compared to warfarin = 0.89 ICH when on aspirin compared to warfarin = 1.00 Death when on no treatment compared to warfarin = 1.65 Death when on NOAC compared to warfarin = 0.89 Death when on aspirin compared to warfarin = 1.04 Stroke having experienced a prior stroke = 4.015		

	Major bleeding having experienced a prior stroke = 1.391 MI having experienced a prior stroke = 1.00 ICH having experienced a prior stroke = 1.632 All-cause mortality having experienced a prior stroke = 1.323 Stroke having experienced a prior major bleeding = 1.323 Major bleeding having experienced a prior major bleeding = 3.320 MI having experienced a prior major bleeding = 1.00 ICH having experienced a prior major bleeding = 3.525 All-cause mortality having experienced a prior major bleeding = 1.323 Stroke having experienced a prior MI = 1.246 Major bleeding having experienced a prior MI = 1.246 MI having experienced a prior MI = 1.00 ICH having experienced a prior MI = 0.942 All-cause mortality having experienced a prior MI = 1.030 Stroke having experienced a prior ICH = 1.786 Major bleeding having experienced a prior ICH = 1.391 MI having experienced a prior ICH = 1.00 ICH having experienced a prior ICH = 10.176		

	All-cause mortality having experienced a prior ICH = 1.323		
Health states	The initial health states in the long-term Markov-cohort model are: - AF with no complications, - Undiagnosed AF, - No AF. Patients in the model may remain in their initial health state, or progress to subsequent health states upon the occurrence of clinical adverse events. Which health states they occupy will be determined by the number of events that they have experienced: 'One event', 'Two events', 'Three events', 'Four events'. When patients die, they enter an absorbing 'Dead' health state, in which they will remain for the duration of the model simulation.	Patients occupy defined health states within the long-term Markov component of the economic model. Patients may either remain in their initial health state, or progress to subsequent health states depending on whether or not they experience clinical adverse events, or die. The first part of the model was defined with the input of clinical experts. This part is flexible and capable of running various scenarios associated with performing initial and subsequent ambulatory monitoring procedures, including waiting time after each monitoring session. The aim was to capture the potential benefits of quick AF detection over 100 days using various ambulatory monitoring technologies. The second part of the model structure was based on previously published studies, including the study by Hill et al, 2020 (15).	Hill et al, 2020 (15)
Sources of unit costs	• Device manufacturer, • NHS reference costs, • BNF, • PSSRU • Previous literature	Unit costs for all resource use estimates in the model were extracted from the literature or obtained through other relevant sources such as NHS Reference Costs (16), Personal Social Services Research Unit (17), British	NHS Reference Costs, 2019 (16) Personal Social Services Research Unit, 2019 (17)

	.	National Formulary (18) and manufacturer price list. Costs were measured in Sterling (£) for the year 2019. Costs derived from other sources included costs of monitoring with the comparator devices, which were sourced from the NICE Medical Technologies Guidance on the Zio device (10), and the costs of complications which were sourced from NICE Technology Appraisal Guidance [TA607] on the use of rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (19), and a previous study by Walker et al, 2016 (20).	British National Formulary, 2019 (18) AliveCor, Inc. NICE MTG52 (10) NICE TA607 (19) Walker et al, 2016 (20)

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

Patients at model entry were those with known, or suspected, AF who are referred for ambulatory ECG monitoring in secondary care. The base-case population was 64 years old. All patients began in the first component of the model, which captured the initial monitoring process using one of the alternative interventions. Output from this model included the costs associated with monitoring, clinical assessment and follow-up monitoring if required, as well as the percentage of diagnoses/missed diagnoses of AF, which determined where patients would enter the long-term Markov-cohort model. The parameters which determined the transition of patients through the initial stage of the model to their final diagnosis are presented in the table below.

Parameters	Mean	Distribution	Lower limit	Upper limit	Source
Transition probabilities					
First stage of the model probabilities: Primary monitoring					
KardiaMobile					
Probability of diagnostic yield	92.79%	Beta	87.76%	96.92%	Hermans et al, 2021 (9)
Probability of AF positive	35.52%	Beta	26.71%	45.11%	Hermans et al, 2021 (9)
Probability of true AF positive	100.00%	Beta	100.00%	100.00%	Hermans et al, 2021 (9)
Probability of true AF negative	100.00%	Beta	100.00%	100.00%	Hermans et al, 2021 (9)
Probability of repeat monitoring after FP	0.00%	Beta	0.00%	0.00%	Assumption
Probability of AF positive - inconclusive	0.00%	Beta	0.00%	0.00%	Assumption
Probability of AF negative - inconclusive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of repeat monitoring after inconclusive	0.00%	Fixed	0.00%	0.00%	Assumption
KardiaMobile + Clinician					
Probability of diagnostic yield	92.79%	Beta	87.76%	96.92%	Hermans et al, 2021 (9)
Probability of AF positive	35.52%	Beta	26.71%	45.11%	Hermans et al, 2021 (9)
Probability of true AF positive	76.50%	Beta	62.00%	88.37%	Hermans et al, 2021 (9)
Probability of true AF negative	99.70%	Beta	97.77%	100.00%	Hermans et al, 2021 (9)
Probability of repeat monitoring after FP	11.06%	Beta	3.32%	22.64%	Hermans et al, 2021 (9)
Probability of AF positive - inconclusive	3.20%	Dirichlet	0.00%	20.99%	Hermans et al, 2021 (9)
Probability of AF negative - inconclusive	94.80%	Dirichlet	73.26%	100.00%	Hermans et al, 2021 (9)
Probability of repeat monitoring after inconclusive	2.00%	Dirichlet	0.00%	16.32%	Hermans et al, 2021 (9)
Holter 24h					
Probability of diagnostic yield	13.25%	Beta	7.71%	19.98%	Hermans et al, 2021 (9)

Probability of AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF negative	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of repeat monitoring after FP	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF positive - inconclusive	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF negative - inconclusive	59.75%	Beta	0.00%	0.00%	Calculation
Probability of repeat monitoring after inconclusive	31.12%	Beta	29.26%	33.74%	Hermans et al, 2021 (9)
Holter 48h					
Probability of diagnostic yield	13.76%	Beta	8.12%	20.60%	Hermans et al, 2021 (9)
Probability of AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF negative	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of repeat monitoring after FP	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF positive - inconclusive	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF negative - inconclusive	59.24%	Beta	0.00%	0.00%	Assumption
Probability of repeat monitoring after inconclusive	31.31%	Beta	29.39%	34.00%	Hermans et al, 2021 (9)
Probability of no AF - inconclusive	76.77%	Beta	0.00%	0.00%	Assumption
Holter 7 days					
Probability of diagnostic yield	14.80%	Beta	8.95%	21.81%	Hermans et al, 2021 (9)
Probability of AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF negative	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of repeat monitoring after FP	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF positive - inconclusive	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF negative - inconclusive	68.31%	Beta	0.00%	0.00%	Calculation
Probability of repeat monitoring after inconclusive	31.69%	Beta	29.65%	34.53%	Calculation
Zio					
Probability of diagnostic yield	16.30%	Beta	6.97%	28.54%	Kaura et al, 2019 (12)
Probability of AF positive	100.00%	Beta	100.00%	100.00%	Assumption
Probability of true AF positive	100.00%	Beta	100.00%	100.00%	Assumption

Probability of true AF negative	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of repeat monitoring after FP	0.00%	Beta	0.00%	0.00%	Assumption
Probability of AF positive - inconclusive	0.00%	Beta	0.00%	0.00%	Assumption
Probability of AF negative - inconclusive	78.96%	Beta	0.00%	0.00%	Assumption
Probability of repeat monitoring after inconclusive	21.04%	Beta	18.90%	24.60%	Calculation
CER					
Probability of diagnostic yield	16.07%	Beta	12.01%	20.59%	Gladstone et al, 2014 (13)
Probability of AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF positive	100.00%	Fixed	100.00%	100.00%	Assumption
Probability of true AF negative	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of repeat monitoring after FP	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF positive - inconclusive	0.00%	Fixed	0.00%	0.00%	Assumption
Probability of AF negative - inconclusive	78.73%	Beta	0.00%	0.00%	Calculation
Probability of repeat monitoring after inconclusive	21.27%	Beta	20.30%	22.50%	Calculation
First stage of the model probabilities: First round of repeat monitoring					
KardiaMobile					
KardiaMobile	100.00%	Fixed	100.00%	100.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
CER	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 24h					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	90.00%	Fixed	90.00%	90.00%	Clinical expert opinion
CER	10.00%	Fixed	10.00%	10.00%	Clinical expert opinion
Holter 48h					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	80.00%	Fixed	80.00%	80.00%	Clinical expert opinion
CER	20.00%	Fixed	20.00%	20.00%	Clinical expert opinion
Holter 7 days					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	60.00%	Fixed	60.00%	60.00%	Clinical expert opinion
CER	40.00%	Fixed	40.00%	40.00%	Clinical expert opinion
Zio					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
CER	100.00%	Fixed	100.00%	100.00%	Clinical expert opinion
First stage of the model probabilities: Second round of repeat monitoring					
KardiaMobile					
KardiaMobile	100.00%	Fixed	100.00%	100.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
CER	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Loop recorder	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 24h					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion

CER	70.00%	Fixed	70.00%	70.00%	Clinical expert opinion
Loop recorder	30.00%	Fixed	30.00%	30.00%	Clinical expert opinion
Holter 48h					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
CER	70.00%	Fixed	70.00%	70.00%	Clinical expert opinion
Loop recorder	30.00%	Fixed	30.00%	30.00%	Clinical expert opinion
Holter 7 days					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
CER	60.00%	Fixed	60.00%	60.00%	Clinical expert opinion
Loop recorder	40.00%	Fixed	40.00%	40.00%	Clinical expert opinion
Zio					
KardiaMobile	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
Holter 7 days	0.00%	Fixed	0.00%	0.00%	Clinical expert opinion
CER	60.00%	Fixed	60.00%	60.00%	Clinical expert opinion
Loop recorder	40.00%	Fixed	40.00%	40.00%	Clinical expert opinion
Proportion of monitoring in primary care	0.00%	Fixed	0.00%	0.00%	Assumption

In the long-term Markov-cohort model, patients began in one of the initial health states ((1) AF with no complications, (2) Undiagnosed AF , (3) No AF) based on their diagnosis from the first stage of the model. The parameters which informed the transition of patients from their initial health state to subsequent 'clinical event' health states are presented in the table below.

Parameters	Mean	Distribution	Lower limit	Upper limit	Source
Treatment pattern for AF detected					
Proportion of patients not receiving treatment	5.00%	Dirichlet	4.00%	6.00%	Clinical expert opinion
Proportion of patients on aspirin	5.00%	Dirichlet	4.00%	6.00%	Clinical expert opinion
Proportion of patients on warfarin	10.00%	Dirichlet	8.00%	12.00%	Clinical expert opinion
Proportion of patients on NOAC	80.00%	Dirichlet	64.00%	96.00%	Clinical expert opinion
Annual risk of clinical adverse events					
Risk of ischemic stroke - AF free patients	5.28%	Beta	4.20%	6.30%	Diamantopoulos et al, 2016 (14)
Risk of ischemic stroke - Undetected AF patients	7.85%	Beta	7.07%	8.64%	Diamantopoulos et al, 2016 (14)
Risk of ischemic stroke - Detected AF patients	3.10%	Beta	2.79%	3.41%	Diamantopoulos et al, 2016 (14)
Risk of ICH - Aspirin	0.55%	Beta	0.495%	0.605%	Diamantopoulos et al, 2016 (14)
Risk of ICH - Warfarin	1.19%	Beta	1.071%	1.309%	Diamantopoulos et al, 2016 (14)
Risk of ICH - NOAC	0.56%	Beta	0.504%	0.616%	Diamantopoulos et al, 2016 (14)
Risk of ICH - Undetected AF patients	0.01%	Beta	0.0081%	0.099%	Hill et al, 2020 (15)
Risk of Major Bleeding - Aspirin	1.15%	Beta	1.035%	1.265%	Diamantopoulos et al, 2016 (14)
Risk of Major Bleeding - Warfarin	1.11%	Beta	0.999%	1.221%	Diamantopoulos et al, 2016 (14)

Risk of Major Bleeding - NOAC	13.40%	Beta	12.06%	14.74%	Diamantopoulos et al, 2016 (14)
Hazard ratios					
HR experiencing stroke – No treatment vs warfarin	3.00	Log Normal	2.40	3.60	Hill et al, 2020 (15)
HR experiencing stroke – NOAC vs warfarin	0.90	Log Normal	0.72	1.08	Hill et al, 2020 (15)
HR experiencing stroke – Aspirin vs warfarin	1.04	Log Normal	0.829	1.243	Assumption, based on risk of MB (Aspirin vs Warfarin) in Diamantopoulos et al, 2016 (14)
HR experiencing major bleeding – No treatment vs warfarin	0.51	Log Normal	0.408	0.612	Hill et al, 2020 (15)
HR experiencing major bleeding – NOAC vs warfarin	0.82	Log Normal	0.656	0.984	Hill et al, 2020 (15)
HR experiencing major bleeding – Aspirin vs warfarin	1.04	Log Normal	0.829	1.243	Assumption, based on risk of MB (Aspirin vs Warfarin) in Diamantopoulos et al, 2016 (14)
HR experiencing MI - NOAC vs warfarin	0.86	Log Normal	0.774	0.946	Hill et al, 2020 (15)
HR experiencing MI - no treatment vs warfarin	0.51	Log Normal	0.459	0.561	Hill et al, 2020 (15)
HR experiencing MI - Aspirin vs warfarin	1.04	Log Normal	0.93	1.14	Assumption, based on risk of MB (Aspirin vs Warfarin) in Diamantopoulos et al, 2016 (14)
HR experiencing ICH – No treatment vs warfarin	1.65	Log Normal	1.320	1.980	Hill et al, 2020 (15)
HR experiencing ICH – NOAC vs warfarin	0.89	Log Normal	0.712	1.068	Hill et al, 2020 (15)
HR experiencing ICH – Aspirin vs warfarin	1.04	Log Normal	0.93	1.14	Assumption, based on risk of MB (Aspirin vs Warfarin) in Diamantopoulos et al, 2016 (14)
HR experiencing death - NOAC vs warfarin	0.89	Log Normal	0.712	1.068	Hill et al, 2020 (15)
HR experiencing death - no treatment vs warfarin	1.65	Log Normal	1.320	1.980	Hill et al, 2020 (15)
HR experiencing death - Aspirin vs warfarin	1.04	Log Normal	0.93	1.14	Assumption
Hazard ratios of experiencing event – base probability					
Stroke	0.012	Log Normal	0.010	0.014	Hill et al, 2020 (15)
Major bleeding	0.066	Log Normal	0.053	0.079	Hill et al, 2020 (15)
MI	0.008	Log Normal	0.006	0.010	Hill et al, 2020 (15)
ICH	0.009	Log Normal	0.007	0.011	Hill et al, 2020 (15)
All-cause mortality	0.038	Log Normal	0.030	0.046	Hill et al, 2020 (15)
Hazard ratios of experiencing stroke – having experienced a prior event					
Prior Stroke	4.015	Log Normal	3.212	4.818	Hill et al, 2020 (15)

Prior Major bleeding	1.323	Log Normal	1.058	1.588	Hill et al, 2020 (15)
Prior MI	1.246	Log Normal	0.997	1.495	Hill et al, 2020 (15)
Prior ICH	1.786	Log Normal	1.429	2.143	Hill et al, 2020 (15)
Hazard ratios of experiencing major bleeding – having experienced a prior event					
Prior Stroke	1.391	Log Normal	1.113	1.669	Hill et al, 2020 (15)
Prior Major bleeding	3.320	Log Normal	2.656	3.984	Hill et al, 2020 (15)
Prior MI	1.246	Log Normal	0.997	1.495	Hill et al, 2020 (15)
Prior ICH	1.391	Log Normal	1.113	1.669	Hill et al, 2020 (15)
Hazard ratios of experiencing MI – having experienced a prior event					
Prior Stroke	1.00	Fixed	1.00	1.00	Hill et al, 2020 (15)
Prior Major bleeding	1.00	Fixed	1.00	1.00	Hill et al, 2020 (15)
Prior MI	1.00	Fixed	1.00	1.00	Hill et al, 2020 (15)
Prior ICH	1.00	Fixed	1.00	1.00	Hill et al, 2020 (15)
Hazard ratios of experiencing ICH – having experienced a prior event					
Prior Stroke	1.632	Log Normal	1.306	1.958	Hill et al, 2020 (15)
Prior Major bleeding	3.525	Log Normal	2.820	4.230	Hill et al, 2020 (15)
Prior MI	0.942	Log Normal	0.754	1.130	Hill et al, 2020 (15)
Prior ICH	10.176	Log Normal	8.141	12.211	Hill et al, 2020 (15)
Hazard ratios of experiencing death – having experienced a prior event					
Prior Stroke	1.323	Log Normal	1.058	1.588	Hill et al, 2020 (15)
Prior Major bleeding	1.323	Log Normal	1.058	1.588	Hill et al, 2020 (15)
Prior MI	1.030	Log Normal	0.824	1.236	Hill et al, 2020 (15)
Prior ICH	1.323	Log Normal	1.058	1.588	Hill et al, 2020 (15)

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Cost of KardiaMobile (device) used in the model = £82.50 (including cost of KardiaMobile hardware and app, as provided by AliveCor®, Inc.). A lifespan of two years was assumed for the device, over which the company guarantees the device performance. Additionally, a period of five days was assumed between episodes, during which the patients should send the device back to the hospital by post. An additional cost of nurse time (10 minutes (5-15) (band 6) at £47 per hour) to prepare use of

the device, and to deliver patient training was factored into the cost of using the technology. Finally, it was assumed that the device would be used up to 38 times over its lifespan, based on information provided by the company. Therefore, the final device cost per monitoring session was calculated to be £8.96. Compared to other devices, KardiaMoile does not incur additional costs of applying and removing monitor + analysis, and reporting of results, while the ECG can be sent to doctors directly.

If the list price is not used in the model, provide the price used and a justification for the difference.

Not applicable.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Included in the table below are the costs associated with defined model health states, interventions, procedures and complications. Their use in the model is described in the text that follows. Relevant values and sources for all costs included in the model are presented below:

Cost	Value (£)	Source
Health service visit costs		
GP visit	39	PSSRU, 2019 (17)
Cardiologist visit	151	NHS Reference Costs, 2019 (16)
Nurse visit time to receive training and preparation of device (minutes)	10 (5-15) at £47 per hour	PSSRU, 2019 (17)
Costs - monitoring		
KardiaMobile (device price)	83	AliveCor®, Inc.
7-day Holter monitoring	171	NICE MTG52 (10)
24-hour Holter monitoring	171	NICE MTG52 (10)
48-hour Holter monitoring	171	NICE MTG52 (10)
14-day Zio	316	NICE MTG52 (10)
CER (per day)	171	NICE MTG52 (10)
Loop recorder	3,280	NICE MTG52 (10)
Costs - anticoagulants		

Aspirin (daily)	0.04	BNF, 2019 (18)
Warfarin (daily)	0.06	BNF, 2019 (18)
NOACs (daily)	1.91	Walker et al, 2016 (20)
Clinical adverse event (year 1)		
Stroke	9,260	NICE TA607 (19)
Major bleed	763	NICE TA607 (19)
ICH	15,251	NICE TA607 (19)
MI	3,736	NICE TA607 (19)
Clinical adverse event (subsequent years)		
Stroke	1,954	NICE TA607 (19)
Major bleed	0	NICE TA607 (19)
ICH	2,922	NICE TA607 (19)
MI	2,098	NICE TA607 (19)
Clinical adverse events (fatal)		
Stroke	2,258	Walker et al, 2016 (20)
Major bleed	2,258	Walker et al, 2016 (20)
ICH	2,258	Walker et al, 2016 (20)
MI	2,258	Walker et al, 2016 (20)

In the first stage of the model, the costs associated with initial health service visits (GP, nurse and cardiologist) were derived from the Personal Social Services Research Unit, 2019 (17) and the NHS Reference Costs, 2019 (16), respectively. The cost of the GP visit was based on a per patient contact of 9.22 minutes. The cost of monitoring patients using the KardiaMobile device was based on information provided by the device manufacturer (AliveCor®). The costs of monitoring with Holter, Zio and of follow-up testing with CER and LR were all sourced from Medical Technologies Guidance of a previous submission of the Zio technology to NICE (10) for the purpose of detecting cardiac arrhythmias.

In the long-term Markov component of the economic model, the costs of treating patients with anticoagulants (if diagnosed with AF) were derived from the British National Formulary, 2019 (18) and from a study by Walker et al, 2016 (20). The costs that patients incurred in clinical event health states were dependent on whether it was the first year of having experienced the event, or if the patient was in a subsequent cycle within that same health state. Where patients died due to experiencing a clinical event, the costs were adjusted to reflect the differing costs associated with a fatal event. All costs associated with clinical adverse events were derived from NICE Technology Appraisal Guidance TA607 (19), which describes the use of Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease, and a previous study by Walker et al, 2016 (20). Where costs were derived from a source prior to 2019, they were inflated accordingly to the current price year.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

See previous section for full details of resources included in the model.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

No additional costs related to use of the technology (other than the cost of the technology itself and the nurse costs associated with preparation of the device, and patient training) are included in the model.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

No additional resources will be required to manage the change in patient outcomes. The model captures the change in clinical outcomes (progression of the condition, as well as occurrence of adverse events) following introduction of the intervention. However, increased resource use will only be required if the intervention results in increased complication rates, and worsens progression of the clinical condition. This is not the case, as complication rates are reduced through introduction of the intervention (see results section). Resource use associated with clinical complications, and health states, included in the model are presented in a later section.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Not applicable. Please see previous paragraph; the same applies to impact on system outcomes.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	Technology costs (£)	Comparator 1, 2, 3 costs (£) (Holter 24h, 48h and 7 days)	Comparator 4 costs (£) (Zio 14 days)	Difference in resource use costs (technology vs comparator 1, 2, 3) (£)	Difference in resource use costs (technology vs comparator 4) (£)
Cost of resource use to implement technology	8.96 (per monitoring session)	171	316	- 162.04	- 307.04
Cost of resource use associated with patient outcomes	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results
Cost of resource use associated with system outcomes	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results
Total costs	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

The following complications (and associated costs) were included in the long-term Markov component of the model, based on the fact that these are the most commonly occurring events amongst this patient population:

(1) Stroke and fatal stroke,
(2) Major bleed and fatal major bleed,
(3) MI and fatal MI,
(4) ICH and fatal ICH.

Complications included in the model had implications for resource use, and quality-of-life and therefore, they were modelled. Please see Table 4 for details on the risk of the different events occurring, and the 'NHS and unit costs' section and Table 6 (following section), for details on costs associated with adverse events.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Note: In the table below the costs of the different clinical complications included in the model have been presented. Due to the fact that the source from which these costs were derived presented costs in an aggregated way, costs have been assigned to 'hospital costs' and 'total costs' in the table below, although it should be noted that these costs include costs associated with staff time and technology/equipment also. These costs are presented per event occurring.

Adverse event	Items	Cost	Source
Cost of stroke (first year)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£9,260	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£9,260	NICE TA607 (19)
Cost of major bleed (first year)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£763	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£763	NICE TA607 (19)
Cost of ICH (first year)	Technology	Text	Text

	Staff	Text	Text
	Hospital costs	£15,251	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£15,251	NICE TA607 (19)
Cost of MI (first year)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£3,736	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£3,736	NICE TA607 (19)
Cost of stroke (subsequent years)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£1,954	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£1,954	NICE TA607 (19)
Cost of major bleed (subsequent years)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£0	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£0	NICE TA607 (19)
Cost of ICH (subsequent years)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£2,922	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£2,922	NICE TA607 (19)
Cost of MI (subsequent years)	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£2,098	NICE TA607 (19)
	[Other items]	Text	Text
	Total	£2,098	NICE TA607 (19)
Cost of fatal stroke	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£2,258	Walker et al, 2016 (20)
	[Other items]	Text	Text
	Total	£2,258	Walker et al, 2016 (20)
Cost of fatal major bleed	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£2,258	Walker et al, 2016 (20)
	[Other items]	Text	Text
	Total	£2,258	Walker et al, 2016 (20)
Cost of fatal ICH	Technology	Text	Text

	Staff	Text	Text
	Hospital costs	£2,258	Walker et al, 2016 (20)
	[Other items]	Text	Text
	Total	£2,258	Walker et al, 2016 (20)
Cost of fatal MI	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£2,258	Walker et al, 2016 (20)
	[Other items]	Text	Text
	Total	£2,258	Walker et al, 2016 (20)

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

Not applicable, all costs included in the model have been presented in previous sections.

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

The device can potentially provide expeditious communication between patients and clinicians in a framework of telemedicine. Therefore, KardiaMobile potentially can be seen as a facilitator to reducing hospital and health care provider pressures and work overload. Future studies are required to capture this potential benefit of KardiaMobile for NHS England.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost (£)	Source
Cost per treatment/patient over lifetime of device	8.96	AliveCor®, Inc., PSSRU, 2019 (17)

Consumables per year (if applicable) and over lifetime of device	0	Not applicable
Maintenance cost per year and over lifetime of device	0	Not applicable
Training cost over lifetime of device	0	Not applicable
Other costs per year and over lifetime of device	0	Not applicable
Total cost per treatment/patient over lifetime of device	0	Not applicable

Table 8 Total costs for the comparator in the model

Description	Cost (£)	Source
Cost per treatment/patient over lifetime of device	171 (comparator 1, 2, 3 – Holter 24 hour, 48 hour and 7 days) 316 (comparator 4 – Zio 14 days)	NICE MTG52 (10)
Consumables per year (if applicable) and over lifetime of device	0	Not applicable
Maintenance cost per year and over lifetime of device	0	Not applicable
Training cost over lifetime of device	0	Not applicable
Other costs per year and over lifetime of device	0	Not applicable
Total cost per treatment/patient over lifetime of device	0	Not applicable

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

In the table below, the cost of the individual resource use components included in the model, associated with each of the included technologies, is presented. Total costs and incremental costs of the intervention, when compared with each of the comparators, are also presented. Costs are presented on an individual patient basis.

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator – Holter 24 hour (£)**	**Mean discounted cost per patient using the comparator – Holter 48 hour (£)**	**Mean discounted cost per patient using the comparator – Holter 7 days (£)**	**Mean discounted cost per patient using the comparator (£) – Zio**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***	**Difference in mean discounted cost per patient (£): technology vs comparator 2***	**Difference in mean discounted cost per patient (£): technology vs comparator 3***	**Difference in mean discounted cost per patient (£): technology vs comparator 4***
Costs of primary AF monitoring	8.96	171.20	171.20	171.20	315.68	-162.24	-162.24	-162.24	-306.72
Costs of repeat monitorings	0.09	123.89	121.16	135.27	74.55	-123.80	-121.07	-135.18	-74.46
Costs of primary care visits	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Costs of secondary care visits	50.28	196.97	196.79	195.18	179.28	-146.69	-146.51	-144.90	-129.00
Costs - Anticoagulants	356.53	241.93	243.08	243.64	226.68	+114.60	+113.44	+112.88	+129.85
Costs of stroke	741.91	789.96	789.48	789.25	796.38	-48.06	-47.58	-47.34	-54.47
Costs of major bleeding	0.85	0.64	0.63	0.61	0.56	+0.22	+0.22	+0.24	+0.29
Costs of ICH	27.14	18.58	18.66	18.70	17.43	+8.56	+8.48	+8.44	+9.71
Costs of MI	23.67	26.18	26.16	26.14	26.51	-2.51	-2.49	-2.47	-2.84
Costs of fatal stroke	47.20	49.78	49.76	49.74	50.13	-2.58	-2.56	-2.54	-2.93
Costs of fatal major bleeding	29.51	24.85	24.90	24.92	24.23	+4.66	+4.61	+4.59	+5.28
Costs of fatal ICH	5.57	4.72	4.72	4.72	4.59	+0.85	+0.85	+0.85	+0.98

Costs of fatal MI	3.58	3.41	3.41	3.41	3.38	+0.18	+0.18	+0.18	+0.20
Costs of two events	1,427.51	1,392.95	1,393.29	1,393.41	1,388.27	+34.57	+34.23	+34.10	+39,24
Costs of three events	219.47	211.25	211.32	211.25	209.97	+8.22	+8.15	+8.22	+9.50
Costs of four events	6.55	6.39	6.39	6.38	6.36	+0.16	+0.16	+0.16	+0.19
Total cost per patient	**2,948.82**	**3,262.69**	**3,260.94**	**3,273.84**	**3,323.99**	**-313.86**	**-312.12**	**-325.01**	**-375.17**
		* Negative values indicate a cost saving. Adapt this table as necessary.							

The economic modelling focussed on impact of introduction of KardiaMobile on health system costs, as well as patients' outcomes (QALYs). Base-case cost results from the model (Table 9) indicate that the technology is cost saving per patient when compared with all included comparators. Table 9 shows the costs for each technology on a per-patient basis, with costs presented for each individual resource use component captured in the model, including costs of monitoring and long-term adverse events. Total costs per patient are less with KardiaMobile than with the comparators modelled. Base-case model results also indicate that introduction of the intervention results in improved patient outcomes when compared with all alternative technologies (see results presented in table below, which shows the incremental life years lived, and incremental QALYs gained, associated with introduction of KardiaMobile over a five-year time horizon). The results show that KardiaMobile results in increased survival, and increased QALYs gained, in all comparisons presented.

Base-case analysis incremental life-years lived and incremental QALYS

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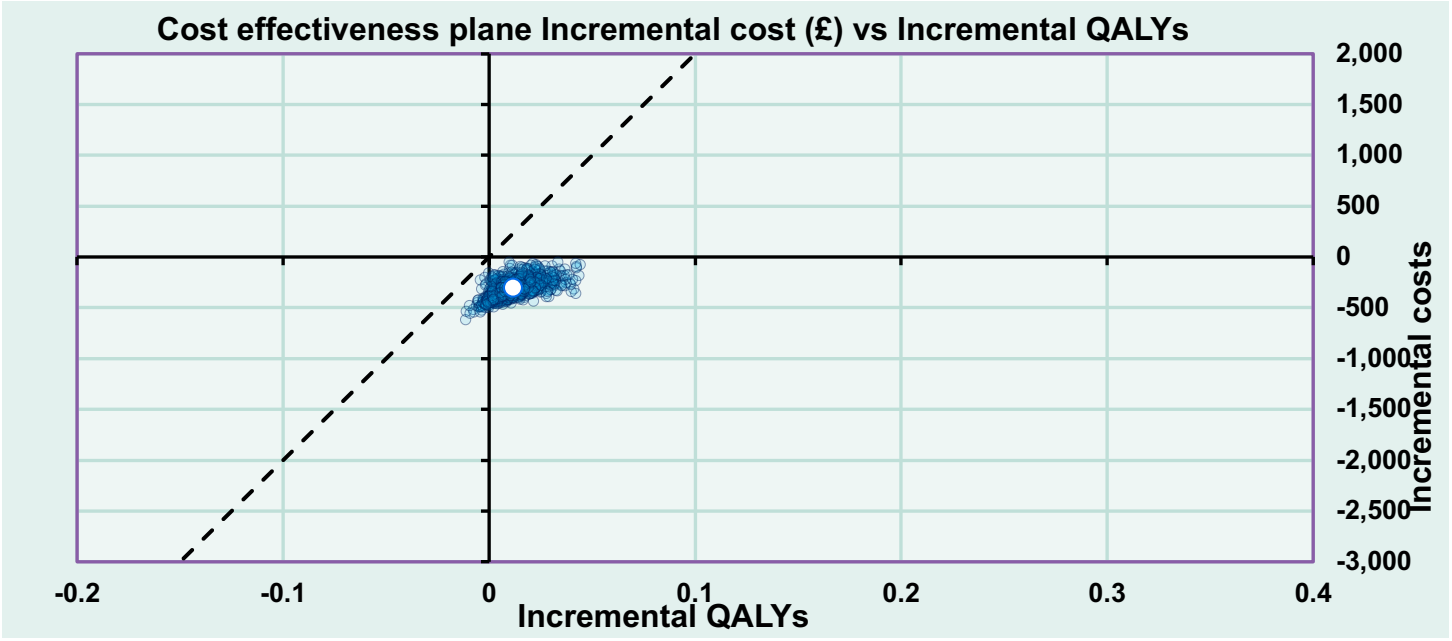
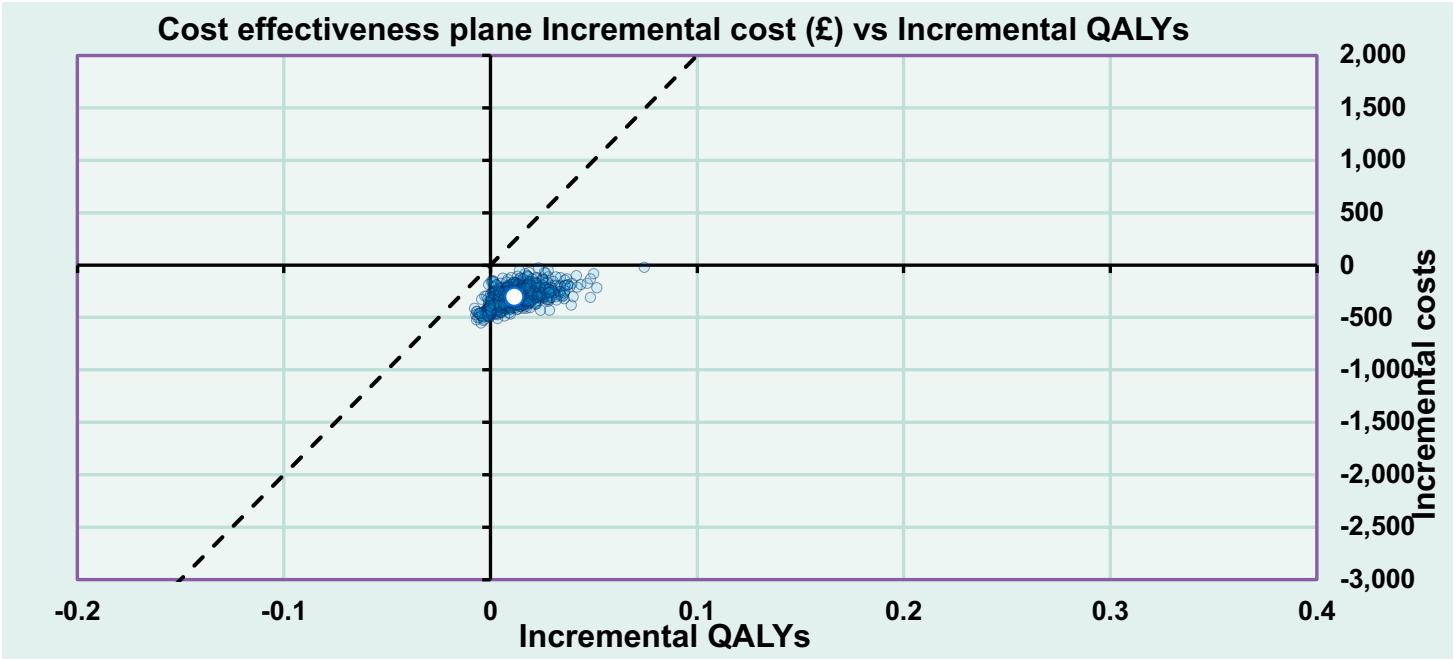
	KardiaMobile	Holter 24h	Holter 48h	Holter 7 days	Zio
Total life years lived	3.48	3.46	3.46	3.46	3.46
Total QALYs	3.275305	3.264111	3.264235	3.264350	3.262728
Incremental life years lived associated with KardiaMobile	----------	+0.018758	+0.018564	+0.018445	+0.021207
Incremental QALYs associated with KardiaMobile	----------	+0.011194	+0.011070	+0.010955	+0.012577

Probabilistic results (which account for uncertainty in the model/parameter estimates based on a number of model simulations) following 1,000 model simulations are presented below. Each graph (cost-effectiveness plane) represents a comparison between KardiaMobile and one of the included comparators. The results show that the majority of points (representing individual iterations of the model) are in the south-east quadrant indicating that the intervention is likely to be less costly and more effective than the comparator in all comparisons.

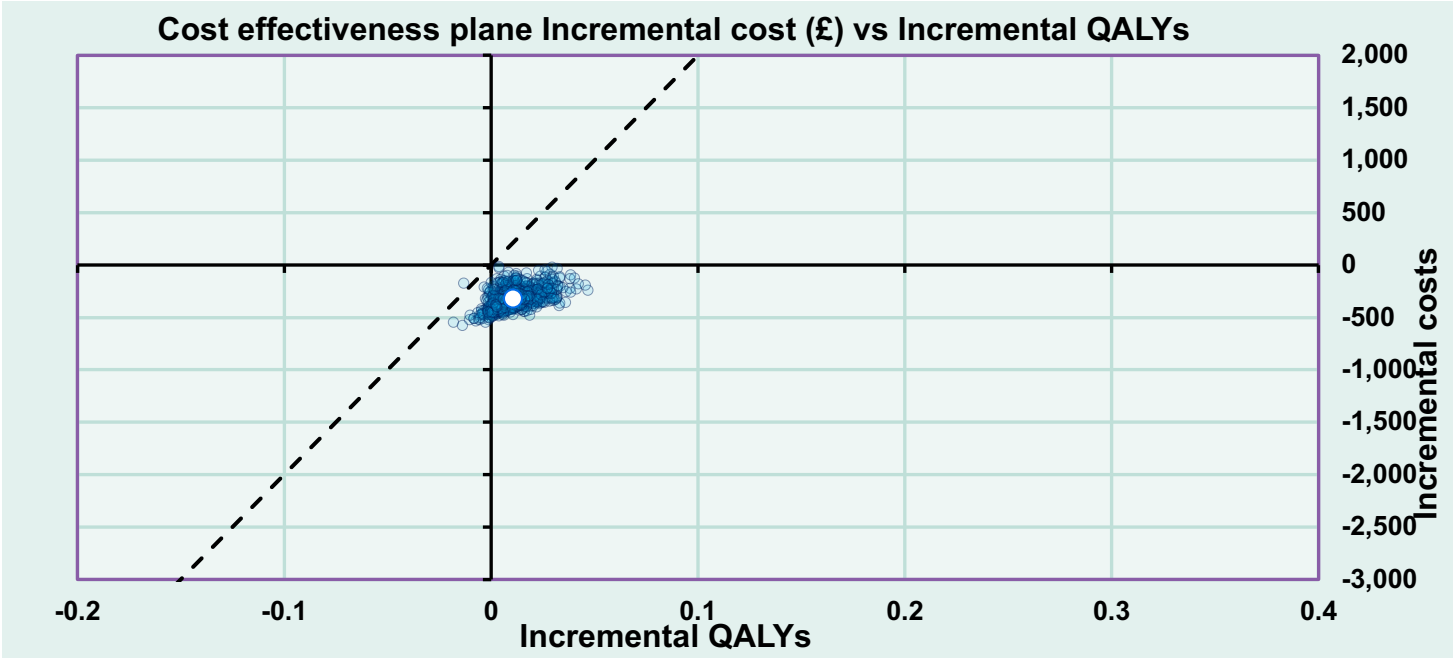
KardiaMobile compared with Holter 24 hour



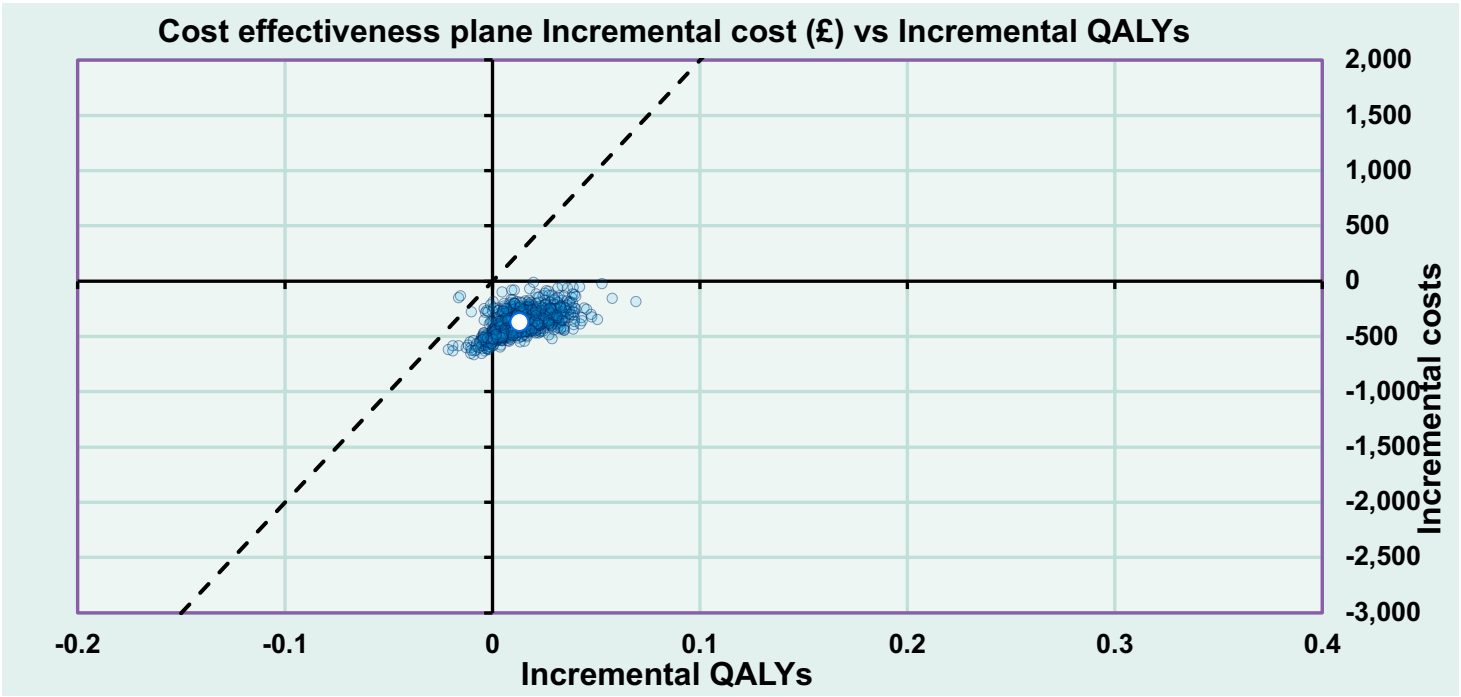
KardiaMobile compared with Holter 48 hour



KardiaMobile compared with Holter 7 days



KardiaMobile compared with Zio



Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

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Various sensitivity analyses exploring uncertainty in model parameters, and impact on the model outputs, are presented in the next section.

One key scenario analysis was conducted to explore the impact of assuming that both positive and inconclusive cases following KardiaMobile monitoring would follow-up with a clinical visit (as opposed to only positive cases, as is assumed in the base-case analysis).

Describe the differences between the base case and each scenario analysis.

Scenario analysis 1

In the base-case analysis, it was assumed that only positive cases following KardiaMobile monitoring would follow-up with a clinical visit. In this scenario, it is assumed that both positive and inconclusive cases are followed-up.

Describe how the scenario analyses were included in the cost analysis.

After exploring variation in the base-case assumption, the overall incremental cost per patient was estimated and reported in the results section below.

Describe the evidence that justifies including any scenario analyses.

Clinical experts advised that this scenario should be explored, to examine the impact that this would have on costs and overall cost-effectiveness of the intervention in a conservative scenario.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

The estimated incremental cost of the intervention compared to each one of the four comparators is presented in the table below (for the base-case analysis (as per the results shown in Table 9) and the scenario analysis outlined above). When it is assumed that both positive and inconclusive cases following KardiaMobile monitoring are followed-up with a clinical visit, the overall cost per patient of receiving KardiaMobile increases from £2,948.82 to £3,039.29. It should be noted that the only resource use

component (as presented in Table 9) that is impacted by this variation is the cost of secondary care visits in the intervention arm of the analysis. Total costs per patient for each of the comparators is not impacted by this variation, as costs in the KardiaMobile arm of the analysis are only affected. Despite the increased cost of KardiaMobile in this analysis, the intervention is still cost saving when compared to each of the comparators (-£223.40 [compared to Holter 24 hour], -£221.65 [compared to Holter 48 hour], -£234.55 [compared to Holter 7 days], -£284.70 [compared to Zio]).

Scenario 1 analysis

Base-case analysis	**Mean discounted cost per patient using the technology (£)**	**Mean discounted cost per patient using the comparator – Holter 24 hour (£)**	**Mean discounted cost per patient using the comparator – Holter 48 hour (£)**	**Mean discounted cost per patient using the comparator – Holter 7 days (£)**	**Mean discounted cost per patient using the comparator (£) – Zio**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***	**Difference in mean discounted cost per patient (£): technology vs comparator 2***	**Difference in mean discounted cost per patient (£): technology vs comparator 3***	**Difference in mean discounted cost per patient (£): technology vs comparator 4***
Total cost per patient	**2,948.82**	**3,262.69**	**3,260.94**	**3,273.84**	**3,323.99**	**-313.86**	**-312.12**	**-325.01**	**-375.17**
Scenario 1 analysis									
Total cost per patient	**3,039.29**	**3,262.69**	**3,260.94**	**3,273.84**	**3,323.99**	**-223.40**	**-221.65**	**-234.55**	**-284.70**
			* Negative values indicate a cost saving. Adapt this table as necessary.						

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Multiple sensitivity analyses were conducted to explore the impact of parameter variations on the model outputs. In the first analysis (multiple one-way sensitivity analyses), all model parameters were varied (increased and decreased) to explore the impact that this had on the incremental cost of the intervention (with results presented in the form of tornado diagrams). If available, the 95% confidence interval for that value was used to inform the variation, and where the confidence interval was unavailable clinical parameters were varied by 20% and cost parameters by 50%. The range of sensitivity analyses are presented in the next paragraph, with results presented afterwards.

In these sensitivity analyses, different values (estimated as described above) have been assigned for all parameters in the model. The results from these sensitivity analyses indicate that in all scenarios the technology is still cost saving which is consistent with the base-case analysis.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Sensitivity analysis:
Multiple one-way sensitivity analyses, in which all model parameters were varied by a defined magnitude (increased and decreased) to look at the impact that this had on the incremental cost of the intervention.

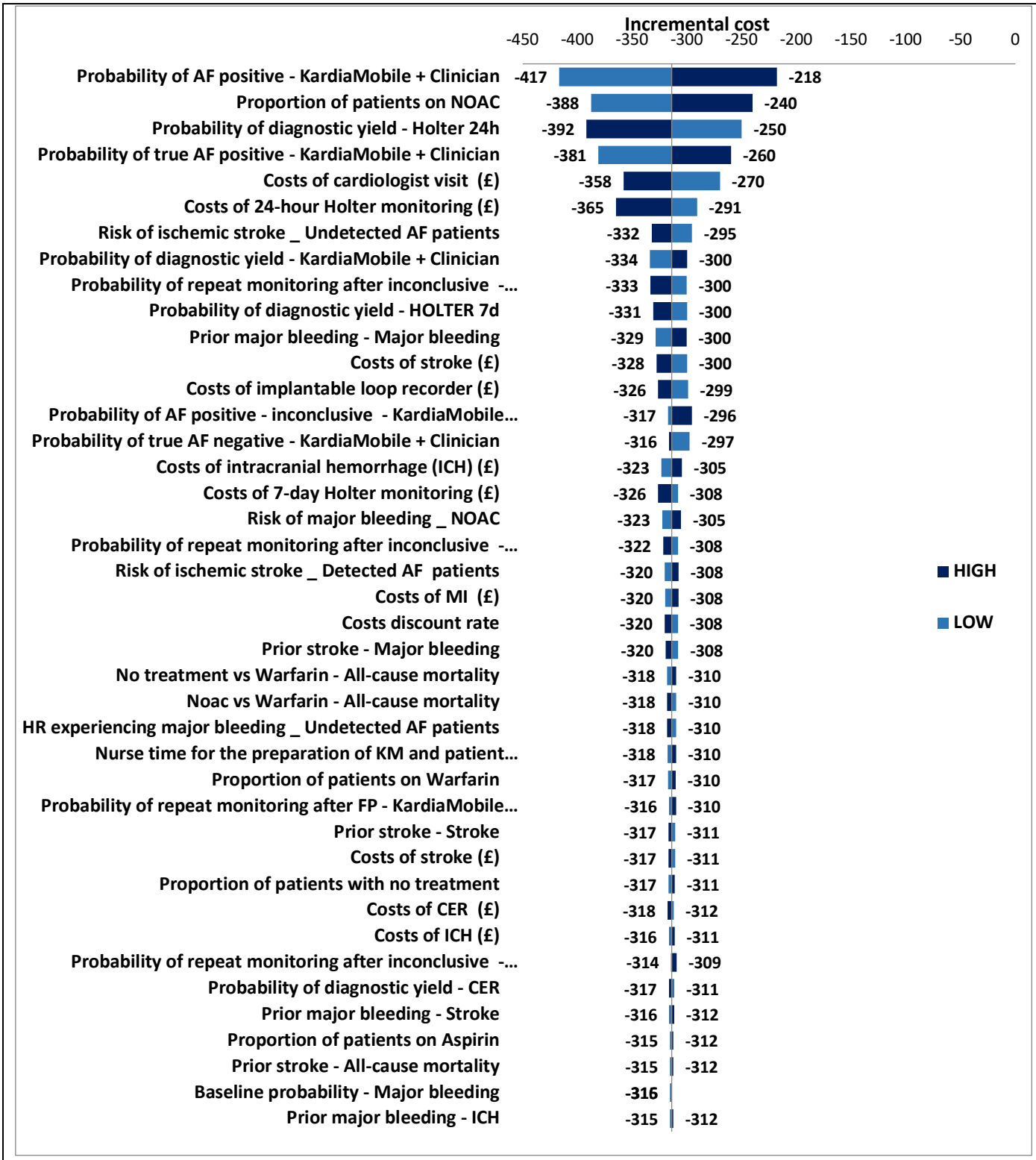
If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All relevant parameters were included in the multiple one-way sensitivity analyses.

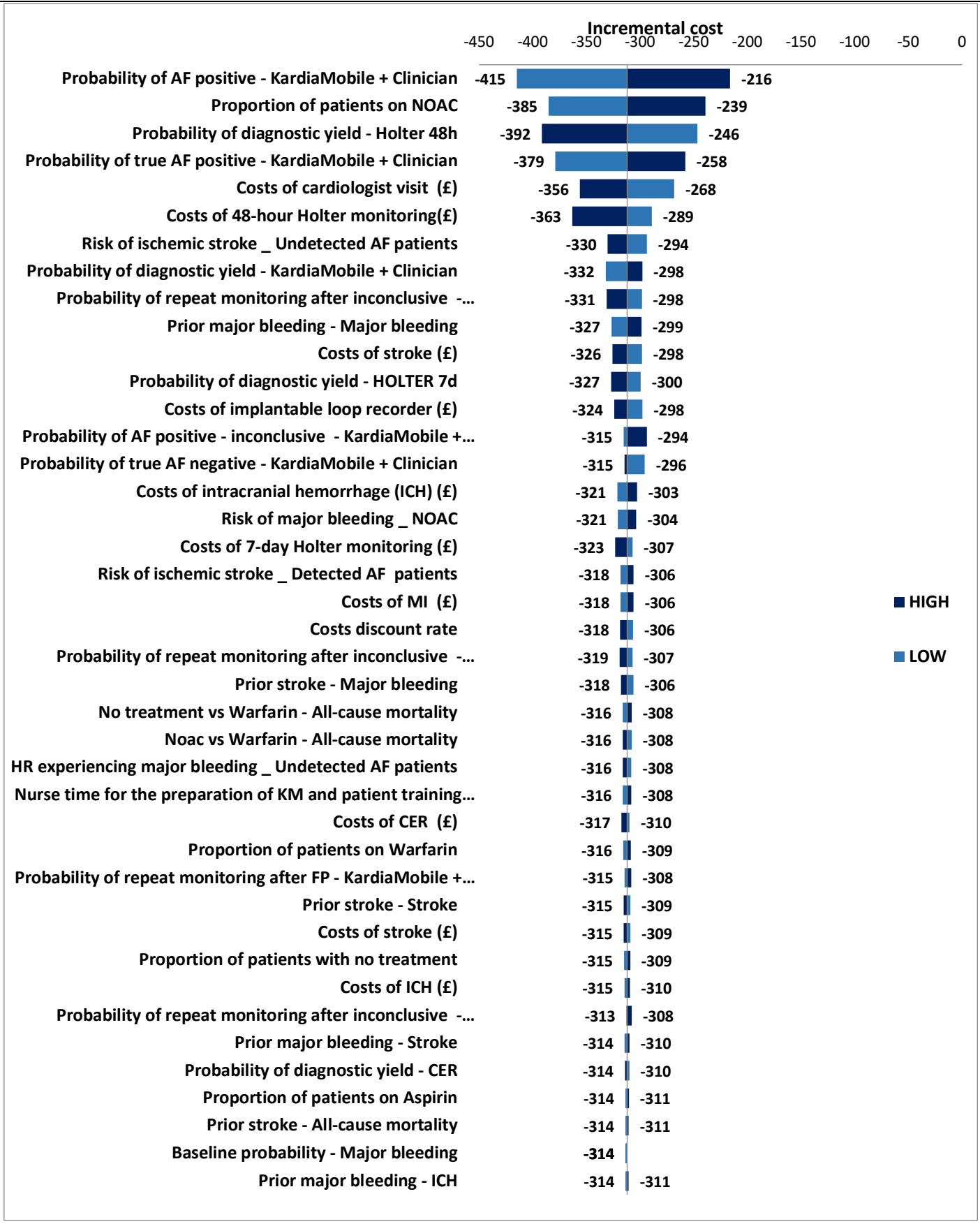
Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

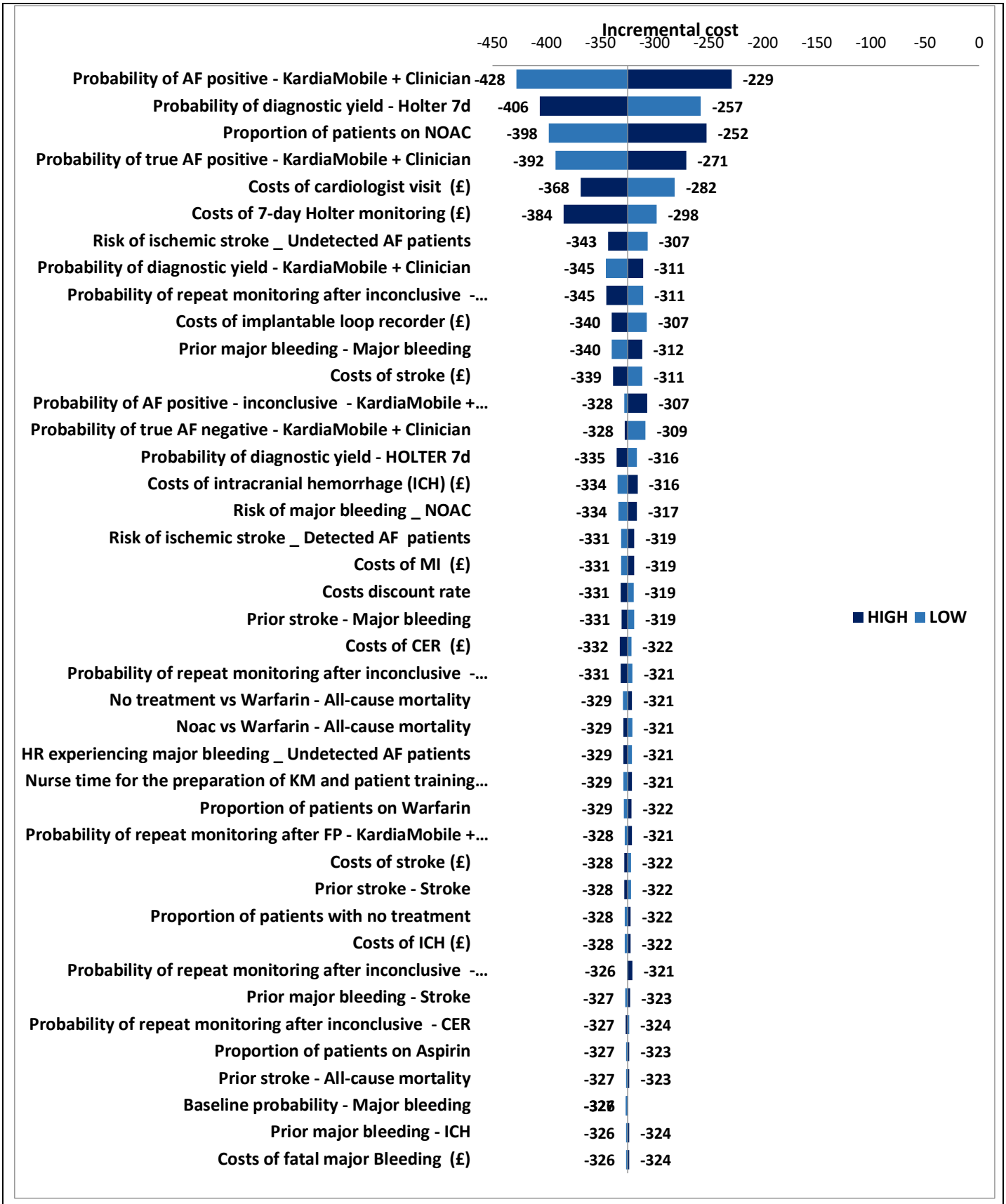
Sensitivity analysis: Impacts of changing values of the input parameters on the estimated incremental cost of the intervention. Tornado diagrams are presented for each comparison below.
KardiaMobile compared with Holter 24 hour



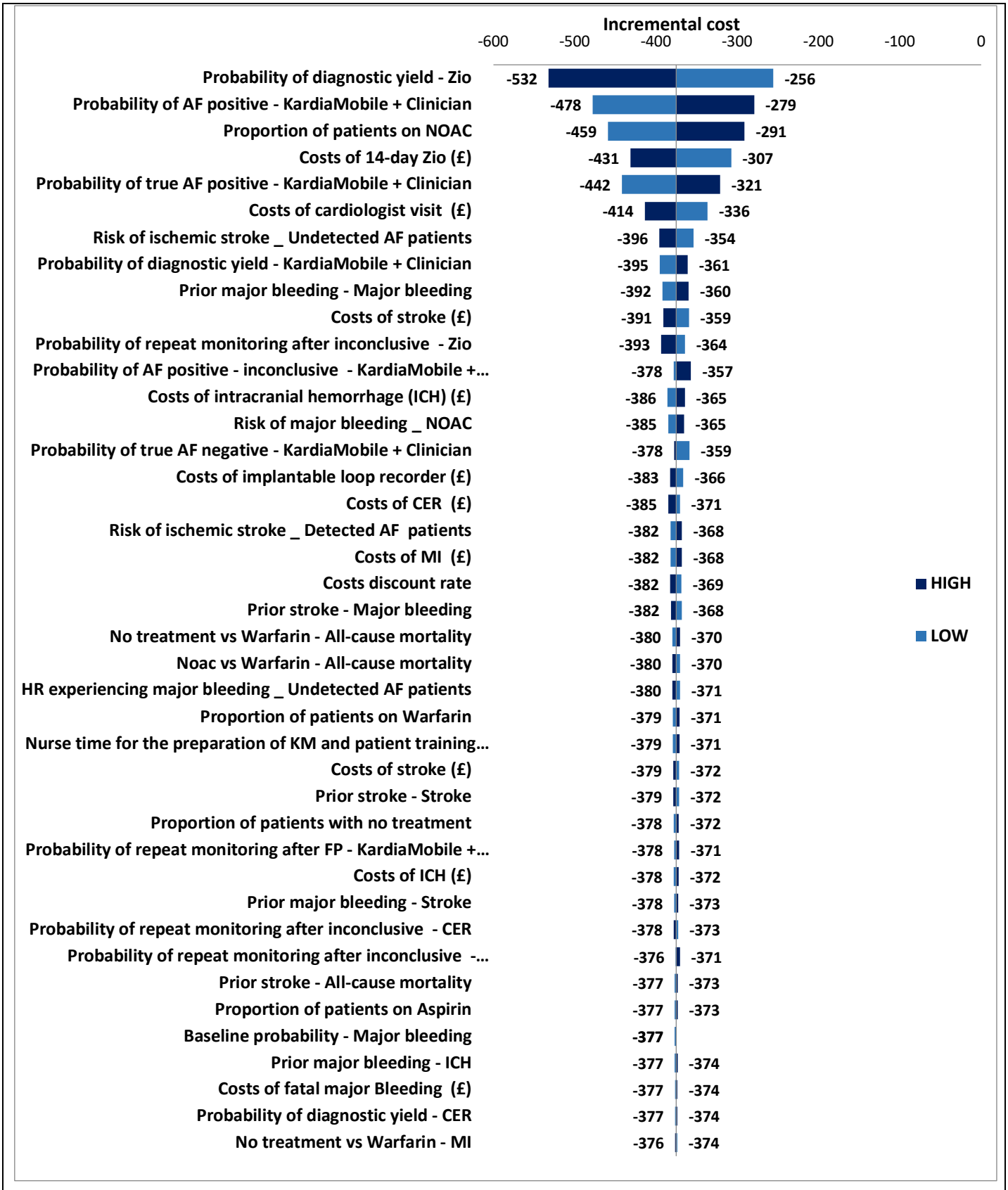
KardiaMobile compared with Holter 48 hour



KardiaMobile compared with Holter 7 days



KardiaMobile compared with Zio



What were the main findings of each of the sensitivity analyses?

Sensitivity analysis: In the tornado diagram(s), which shows the results of the multiple one-way sensitivity analyses (parameter variations), parameters are displayed in order, with those which have the greatest impact on incremental cost displayed at the top and those with have the least impact displayed at the bottom of the graph. Four tornado diagrams are presented in the results above, each one representing a comparison between KardiaMobile and one of the four comparators included in the analysis. In all four diagrams, the results show that the parameters which have the largest impact on cost results are the diagnostic yield associated with the comparator, the proportion of patients on NOAC, and the probability of being AF positive following KardiaMobile monitoring.

Results from the sensitivity analyses highlighted above show the parameters which have the greatest impact on the incremental cost of the intervention. Notably, in all four analyses, regardless of the variation made to all included model parameters, the overall conclusion (i.e., KardiaMobile is a cost saving intervention) remains the same.

What are the main sources of uncertainty about the model's conclusions?

As described in detail in the later section, there is uncertainty surrounding the values associated with a select number of model parameters (please refer to Section 4). However, extensive sensitivity analyses were conducted with little impact on the overall results identified.

Miscellaneous results

Include any other relevant results here.

Not applicable.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

In order to evaluate the face validity of the model, the model structure, input parameters and results were presented to clinical experts with significant experience working in this clinical area, and who are well-respected in this field of research. They evaluated the model structure and assumptions in comparison to real-world circumstances. A large number of sensitivity analyses were also conducted to assess the internal validity of the model. Null and extreme values were assigned to input parameters and the model was run to test the robustness of the results.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Dr Yassir Javaid GP with specialist interest in cardiology, Cardiovascular and Diabetes Lead at Nene CCG, Cardiovascular lead at East Midlands Clinical Network, and Clinical Adviser for Cardiology with RCGP Contact: yassir.javaid@nhs.net

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Findings from the economic modelling indicate that introduction of the technology results in cost savings for the health care service in England and improved patient outcomes (both a reduction in the clinical complication rate, and an increase in quality-adjusted life-years gained). A probabilistic model was developed, which allows one to quantify the uncertainty present in the model results. However, based on 1,000 iterations of the model, results indicate that the intervention is likely to be cost saving and more effective than all comparators included in the analysis. Base-case model results indicate that cost savings of £312-£376 per patient (depending on comparator chosen) would be made over a five-year time horizon, as well an increase of 0.011-0.013 QALYs per patient (depending on comparator chosen). Therefore, the intervention can be considered to be a 'dominant' strategy in that it is less costly and more effective than the comparator(s).

Following introduction of KardiaMobile, cost savings are largely driven by a reductuion in the number of health care service visits, and associated costs, related to ambulatory monitoring in the short-term. The model output also indicates that introduction of the intervention reduces the costs, and clinical event rate, associated with stroke and MI. These events are associated with high treatment and management costs. Thus, both short- and long-term health care cost savings are projected.

In summary, the high costs associated with existing methods of monitoring AF, and associated long-term complication costs, when viewed against a relatively low technology acquisition cost for KardiaMobile (£82.50 per device and £8.96 per monitoring session) results in meaningful improvements to patient quality-of-life and clinical outcomes as well as a significant reduction in healthcare burden.

Briefly discuss the relevance of the evidence base to the scope.

Appropriately monitoring, diagnosing, and subsequently managing AF is increasingly important due to the significant health care costs associated with the condition and the detrimental impact that it can have on patient's quality-of-life. From an economic perspective, existing methods to monitor and diagnose the condition are costly, while incorrect diagnoses can lead to poor clinical outcomes over the long-term, which result in patient morbidity, mortality, and high health care costs.

KardiaMobile is an innovative technology which offers an alternative to the existing AF diagnostic pathway, by allowing patients to capture a medical-grade ECG quickly and easily from wherever they are located. With the press of a button, results can be saved and shared with a doctor for interpretation, leading to quicker diagnoses and reducing unnecessary use of health care services.

A robust decision-analytic model indicates that introduction of KardiaMobile in the diagnostic pathway is less costly and more effective in reducing the health care burden associated with AF compared to current standard of care amongst patients with known, or suspected, AF who are referred for ambulatory ECG monitoring in the NHS. These findings are further supported by real-world evidence summarized herein in the target demographic undergoing monitoring. Therefore, the evidence provided directly aligns with the scope.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

One abstract involving a cost analysis of KardiaMobile was identified in the search for economic evidence. The US study by Goel et al, 208 (5) reported a cost per device of $99. The authors did not undertake further cost analyses, or cost-effectiveness analyses, other than to report the cost of the device. While they highlight that KardiaMobile is likely to be a cost-efficient use of health service resources due to its low cost and superior, or concordant, diagnostic performance compared with Holter monitoring (as demonstrated in the study), the results are largely incomparable to the economic analysis that is presented here.

Four full-text publications were identified in the search for relevant economic evidence. The study by Praus et al, 2020 (1) looked at the potential cost savings that could be realised due to the reduction in healthcare utilization associated with use of the KardiaMobile device. They calculated that the avoidance of ED visits through the quality improvement project being evaluated (which involved use of KardiaMobile) resulted in cost savings of $81,950. The study by Halcox et al, 2017 (2) conducted a detailed breakdown of the costs associated with twice-weekly monitoring with the KardiaMobile device. Overall, they estimated that the cost per AF diagnosis was $10,780 (£8,255). The economic impact evaluation case study of the KardiaMobile device conducted by the York Health Economics Consortium (3) carried out a cost comparison of introducing KardiaMobile in the diagnostic pathway for AF. They performed a simple return on investment calculation and estimated that use of the intervention would result in savings of £968 per patient from an NHS perspective. They estimated that if 250 patients per year followed the Kardia pathway rather than the typical diagnostic pathway, the value of the savings would be £242,000 per year. The final identified full-text study by Reed et al, 2019 (4) estimated that the cost per symptomatic rhythm diagnosis would be £921 less per patient per symptomatic rhythm in the intervention group (£474) compared to the control group (£1395), in their comparison of KardiaMobile with standard care.

The results of all identified cost analyses are consistent with the results of the economic analysis presented here, in that they demonstrate the cost-saving potential of KardiaMobile. However, none of the studies described above involved a long-term cost-effectiveness analysis focussing on clinical outcomes over a number of years, including health-related quality-of-life. While none look at long-term cost-effectiveness, or impact on quality-of-life, associated with introduction of KardiaMobile (as we have presented in our model), all show the potential for the intervention to reduce unnecessary healthcare utilization. Additionally, while the results of the identified studies are consistent, we consider this economic analysis of KardiaMobile to be the strongest demonstration of the long-term potential for cost savings and improved patient outcomes.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The analysis is relevant to all patients with known, or suspected, AF who are referred for ambulatory ECG monitoring in the NHS.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths:

A robust decision-analytic model was developed, which accounts for the uncertainty present through the probabilistic nature of the analysis. Additionally, as described, extensive sensitivity analyses have been conducted to explore the impact of individual, and multiple, parameter variation on the results of the economic analysis. The model was informed by clinical guidelines, published literature and expert clinical input, and any assumptions that were made in the analysis can be rectified by using more robust data in later studies, as a model now exists for re-analysis once additional information becomes available. It should be noted however that the direct comparison with Holter monitoring, and the detailed information presented in Hermans et al, 2021 (9) proved a robust source of data for inclusion in this economic analysis.

Limitations:

Limitations of this analysis were as follows:

- There was a relative lack of large head-to-head comparisons of the KardiaMobile device with Zio patch.
- Despite a well-designed study by Hermans et al, 2021 (9) being utilised in this analysis, the study is focused on the post-ablation population. Additionally, the source of clinical data for Zio patch (Kaura et al, 2019 (12)) is focused on the post-stroke population.
- Clinical expert input was relied upon to inform the probabilities of subsequent ambulatory monitoring and the switching pattern between different technologies, due to lack of data available to inform these model parameters.

Despite the above limitations, the base-case analysis results, and the results of sensitivity analyses, indicated that the magnitude of demonstrated savings is sufficiently large to suggest that only major variations in input parameter values are likely to change the conclusions of the analysis.

Detail any further analyses that could be done to improve the reliability of the results.

The structure of the economic model, and the methods used, are robust enough to allow for re-analysis. Further analyses should focus on identifying more reliable data to inform the parameters outlined in the limitations above.

5 References

Please include all references below using NICE's standard referencing style.

1. Praus, T., Li, J., Barbarash, S., et al. Improving care for patients with atrial fibrillation through the use of a personal electrocardiogram, 2020. Journal of the American Association of Nurse Practitioners (2021) 1–7.
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6. Excellence NIfHaC. Guide to the methods of technology appraisal 2013 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.
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17. Curtis L, Burns A. Unit Costs of Health and Social Care 2019, Personal Social Services Research Unit, University of Kent, Canterbury 2019 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/.
18. British National Formulary. 2019 [Available from: https://www.bnf.org/].

19. NICE Technology Appraisal Guidance 607 [TA607]. Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease, 2019.
20. Walker S, Asaria M, Manca A, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). European Heart Journal-Quality of Care and Clinical Outcomes 2016;2(2):125-40.

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	30/03/2021 & 01/04/2021
Date span of search:	Until 30/03/2021 & 01/04/2021

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Database: PUBMED (All fields) <To 30th March, 2021>

		Result
1	((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR (non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)	89,761
2	((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro)	20,214
3	#2 AND #3	605
4	((((((((((((((((((economics/)) OR (value of life/)) OR (exp "costs and cost analysis"/)) OR (exp economics, hospital/)) OR (exp economics, medical/)) OR (exp resource allocation/)) OR (economics, nursing/)) OR (economics, pharmaceutical/)) OR (exp "fees and charges"/)) OR (exp budgets/)) OR (budget*.ti,ab.)) OR (cost*.ti,ab.)) OR ((economic* or pharmaco?economic*).ti,ab.)) OR ((price* or pricing*).ti,ab.)) OR ((financ* or fee or fees or expenditure* or saving*).ti,ab.)) OR ((value adj2 (money or monetary)).ti,ab.)) OR (resourc* allocat*.ti,ab.)) OR ((fund or funds or funding* or funded).ti,ab.)) OR ((ration or rations or rationing* or rationed).ti,ab.)	1,878,757
	3 AND 4	62

Database: EMBASE (All fields, <To 30th March, 2021>)

		Result
1	((((((((((((((((((((((atrial fibrillation) OR (atrium fibrillation)) OR (auricular fibrilation)) OR (auricular fibrillation)) OR (cardiac atrial fibrillation)) OR (cardiac atrium fibrillation)) OR (fibrillation, heart atrium)) OR (heart atrial fibrillation)) OR (heart atrium fibrillation)) OR (heart fibrillation atrium)) OR	180,712

	(non-valvular atrial fibrillation)) OR (nonvalvular atrial fibrillation)) OR (chronic atrial fibrillation)) OR (chronic atrium fibrillation)) OR (paroxysmal atrial fibrillation)) OR (paroxysmal heart atrium fibrillation)) OR (permanent atrial fibrillation)) OR (permanent atrium fibrillation)) OR (persistent atrial fibrillation)) OR (persistent atrium fibrillation)) OR (persistent heart atrium fibrillation)) OR (acute atrial fibrillation)) OR (acute heart atrium fibrillation)) OR (new-onset atrial fibrillation)) OR (recent-onset atrial fibrillation)	
2	((((((((((((((((KardiaMobile) OR (Kardia mobile)) OR (Kardiaband)) OR (Kardia band)) OR (Kardiaapp)) OR (Kardia app)) OR (AliveCor)) OR (KardiaMobile 6l)) OR (Self-recording ECG)) OR (Mobile AF)) OR (Mobile monitoring)) OR (Single lead ECG)) OR (Portable single lead ECG)) OR (Single lead ECG recorder)) OR (Portable single lead ECG recorder)) OR (Wearable rhythm recording)) OR (Kardia)) OR (Zenicor-ECG)) OR (KardiaPro)	1,046
3	#2 AND #3	360
4	((((((((((((((((((economics/)) OR (value of life/)) OR (exp "costs and cost analysis"/)) OR (exp economics, hospital/)) OR (exp economics, medical/)) OR (exp resource allocation/)) OR (economics, nursing/)) OR (economics, pharmaceutical/)) OR (exp "fees and charges"/)) OR (exp budgets/)) OR (budget*.ti,ab.)) OR (cost*.ti,ab.)) OR ((economic* or pharmaco?economic*).ti,ab.)) OR ((price* or pricing*).ti,ab.)) OR ((financ* or fee or fees or expenditure* or saving*).ti,ab.)) OR ((value adj2 (money or monetary)).ti,ab.)) OR (resourc* allocat*.ti,ab.)) OR ((fund or funds or funding* or funded).ti,ab.)) OR ((ration or rations or rationing* or rationed).ti,ab.)	2,203,424
	3 AND 4	72

Database: NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Effects (DARE) and Health Technology Assessments (HTA) via CRD Database <to April 01, 2021>

		Result
1	KardiaMobile OR kardia mobile OR AliveCor OR self-recording ecg OR KardiaMobile 6l OR mobile monitoring OR single lead ecg OR portable single lead ecg OR single lead ecg recorder OR portable single lead ecg recorder OR wearable rhythm recording OR kardia OR zenicor ecg OR kardiapro OR kardiaapp OR kardia app.	1

Database: Cost-Effectiveness Analysis registry (CEA registry) via Centre for the Evaluation of Value and Risk in Health <to April 01, 2021>

		Result
1	KardiaMobile OR kardia mobile OR AliveCor OR self-recording ecg OR KardiaMobile 6l OR mobile monitoring OR single lead ecg OR portable single lead ecg OR single lead ecg recorder OR portable single lead ecg recorder OR wearable rhythm recording OR kardia OR zenicor ecg OR kardiapro OR kardiaapp OR kardia app.	1

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

References of the identified studies were also checked for relevant studies. In addition, we searched a list of 'Clinical Research & Other Supporting Literature' provided to us by the company which contained details of all relevant clinical and economic literature associated with the technology.

Inclusion and exclusion criteria:

Inclusion criteria

Population: The target population for this review were adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care.

Intervention: The KardiaMobile system: KardiaMobile hardware (single-lead or 6 lead ECG monitor) and KardiaMobile app. Single time point detection of atrial fibrillation was not included in the scope of this evaluation.

Comparator(s): Current pathways for atrial fibrillation detection, which include ECG (a 12-lead ECG, performed and interpreted by a trained healthcare professional, which is the reference standard for assessing diagnostic accuracy) and ambulatory monitoring (Holter and/or event monitoring).

Outcomes: Relevant health outcomes included:

- Life-years gained,
- Quality-adjusted life-years (QALYs) gained,
- Incremental cost-effectiveness ratios (ICERs),
- Clinical effectiveness (e.g., survival rates, healing rates, etc.),
- Details of the results of sensitivity analyses.

Country: No limitation of included studies based on study country. All studies meeting the inclusion criteria which were conducted in any country were included in the review.

Language: Only studies with full text in English were included in this review. Studies with abstracts in English but full text published in any language other than English were excluded.

Publication timeframe: All studies published from database start to present were included in this review in order to obtain all available evidence.

Study design: The study designs to be included in this systematic review were economic evaluations (cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-consequence analyses, cost-minimisation analyses), budget impact models, and cost analysis studies.

Exclusion criteria

Studies to be excluded included those that did not have a cost/economic analysis, i.e., were not an appropriate study design, and/or did not meet the inclusion criteria in terms of population, intervention, comparator(s), outcomes reported or language.

Data abstraction strategy:

Data from all included studies were extracted using a pre-designed form. Data extraction was undertaken by one reviewer and checked by a second reviewer. Disagreements between the review authors were resolved by discussion and consensus, with involvement of a third review author where necessary.

The authors of each original study would be consulted when there was incomplete or missing relevant data, although this was not necessary. The table below outlines the relevant categories and specific data that were extracted from all studies that met the inclusion criteria.

Outcome categories	Relevant outcomes
Study details	• Study name • Year of publication • Cost year and currency(ies) • Study design • Country(ies) • Intervention and comparator details • Type of evaluation
Population characteristics	• Mean/median age • Comorbidities
Modeling methodologies	• Perspective (e.g., healthcare payer, societal) • Time horizon • Discounting • Markov or decision tree or other types • Cycle length • Health state names (if applicable) • Simulation method (e.g., cohort, patient-level) • Sensitivity analyses type • Model assumptions • Mortality modelling
Model structure, key data sources and risk equations	• Incorporation of treatment effects • Incorporation of complications/adverse events • Incorporation of health-related quality-of-life • Incorporation of resource use and costs
Input source	• Input source for resource use • Input source for unit costs • Input source for clinical effectiveness • Input source for health utility/quality-of-life
Outcomes	• Life-years gained • Quality-adjusted life-years gained (QALYs) • Incremental cost-effectiveness ratios (ICERs) • Clinical effectiveness (survival rates, healing rates etc.) • Details of sensitivity analyses results

Excluded studies

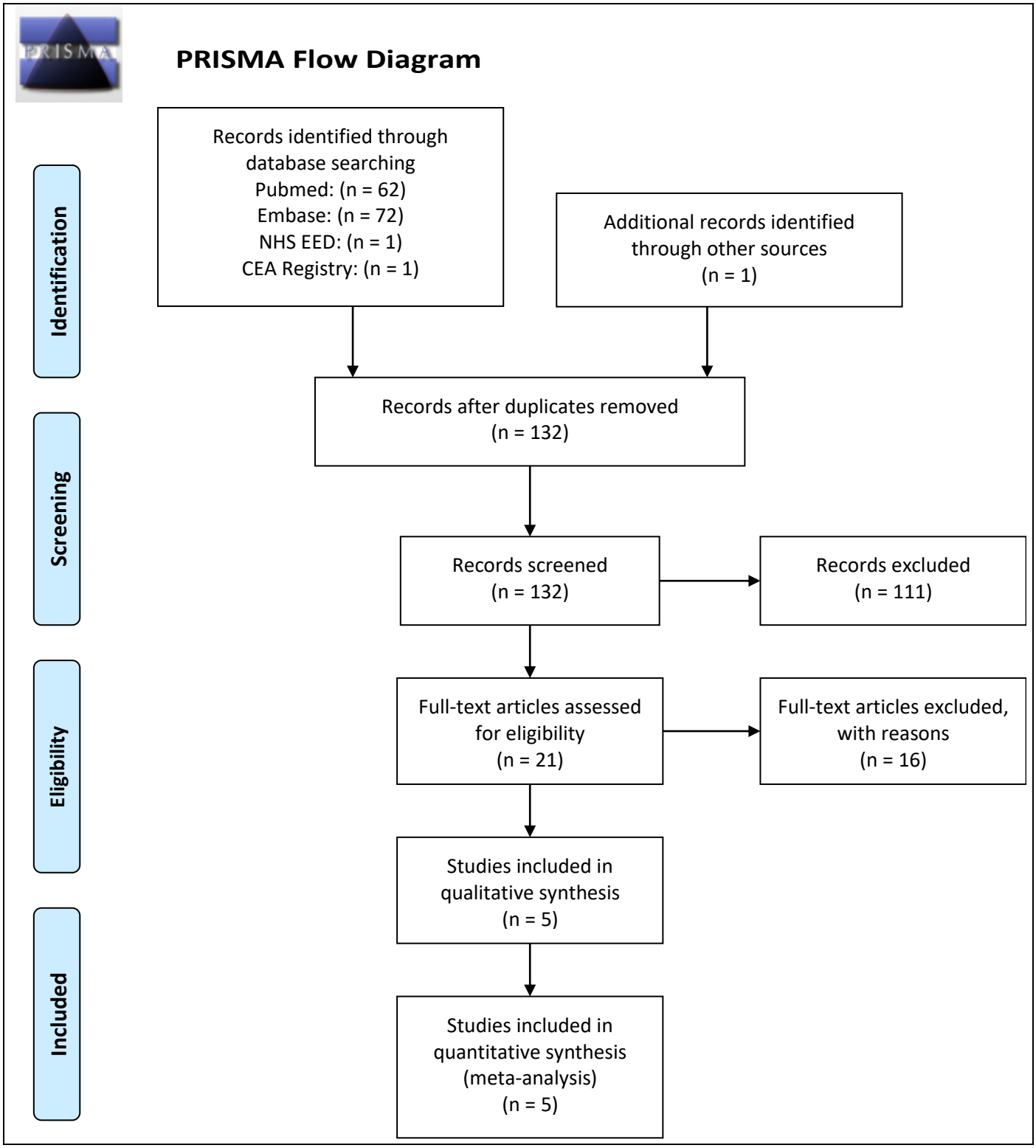
List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Use of mHealth Devices to Screen for Atrial Fibrillation: Cost-Effectiveness Analysis	Cost-effectiveness analysis of mHealth device	Does not relate to KardiaMobile device specifically	None
Atrial Fibrillation Screen, Management, and Guideline-Recommended Therapy in the Rural Primary Care Setting: A Cross-Sectional Study and Cost-Effectiveness Analysis of eHealth Tools to Support All Stages of Screening	Cross-sectional study and cost-effectiveness analysis of population screening for AF	Involves use of the device at a single time-point assessment	None
Opportunistic screening for atrial fibrillation by clinical pharmacists in UK general practice during the influenza vaccination season: A cross-sectional feasibility study	Cross-sectional feasibility study of the KardiaMobile device	Involves use of the device at a single time-point assessment	None
Lead-I ECG for detecting atrial fibrillation in patients with an irregular pulse using single time point testing: a systematic review and economic evaluation	Systematic review and economic evaluation of multiple devices, including KardiaMobile	Involves use of the device at a single time-point assessment	None
Is Screening for Atrial Fibrillation in Canadian Family Practices Cost-Effective in Patients 65 Years and Older?	Cost-effectiveness analysis of a single-lead ECG	Does not relate to KardiaMobile device specifically	None
Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis	Systematic review and economic evaluation of multiple devices, including KardiaMobile	Involves use of the device at a single time-point assessment	None
Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-	Cost-effectiveness analysis of a single-lead ECG	Does not relate to KardiaMobile device specifically	None

lead electrocardiogram device in the Netherlands			
Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting	Clinical and economic analysis of KardiaMobile compared with MyDiagnostick	Involves use of the device at a single time-point assessment	None
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study	RCT and cost-effectiveness analysis	Does not relate to KardiaMobile device specifically	None
Connected health remote monitoring in atrial fibrillation care management.	Pilot study of use of the KardiaMobile device in screening for AF	Does not involve a cost/economic analysis	None
Cost-Effectiveness of Extended and One-Time Screening Versus No Screening for Non-Valvular Atrial Fibrillation in the USA.	Cost-effectiveness analysis of Zenicor single-lead ECG	Does not relate to KardiaMobile device specifically	None
Budget impact analysis of one-time screening for atrial fibrillation.	Budget impact of analysis of screening for AF	Involves use of the device at a single time-point assessment, and does not relate to KardiaMobile specifically	None
An RCT to determine if screening for paroxysmal atrial fibrillation reduces stroke and mortality: The safer programme-screening for atrial fibrillation with ECG to reduce stroke.	RCT of screening for AF with Zenicor	Does not relate to KardiaMobile device specifically	None
Population screening for atrial fibrillation: Results of a cost-effectiveness modelling analysis.	Cost-effectiveness analysis of screening for AF with KardiaMobile	Involves use of the device at a single time-point assessment	None
Accuracy and cost-effectiveness of two handheld electrocardiogram recorders to screen for	Cost-effectiveness analysis involving use of KardiaMobile	Involves use of the device at a single time-point assessment	None

atrial fibrillation in a hospital setting.			
Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: The SEARCH-AF study.	Feasibility study and cost-effectiveness analysis of screening with KardiaMobile in the community setting	Involves use of the device at a single time-point assessment	None

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



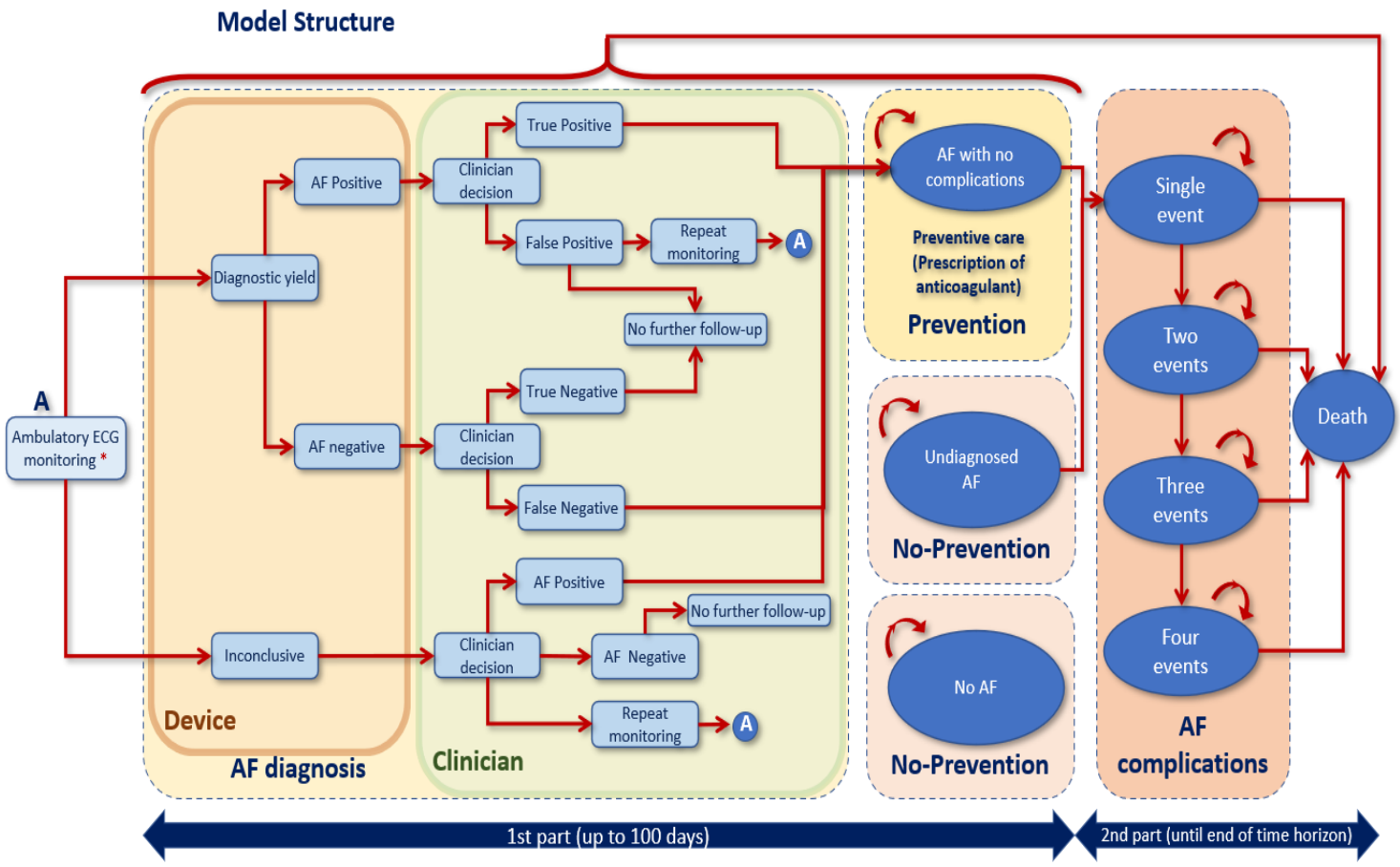
Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods

Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

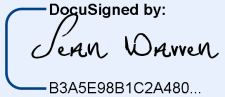
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	
Details	Model structure		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	28/04/2021
Print:	Sean Warren	**Role / organisation:**	AliveCor Ltd Business Director UK&I

Contact email: sean.warren@alivecor.com

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance:

Expert contact details and declarations of interest:

Expert #1	Adrian Brodison, Clinical lead cardiology, University hospitals of morecambe bay NHSFT, [redacted]
	Nominated by:
	DOI: NONE
Expert #2	David Ferguson, Arrhythmia Advanced Nurse Practitioner, University Hospitals of Morecambe Bay NHS Foundation Trust, [redacted]
	Nominated by: Expert above
	DOI: NONE
Expert #3	Kevin McGibbon, Arrhythmia CNS, NHS, [redacted]
	Nominated by company :
	DOI: YES AliveCor/KardiaM.obile have approached me and I have agreed to film a testimonial by healthcare professional that they may be using in their TV/social media adverts for the device. There is no payment involved.
Expert #4	Lis Neubeck, Professor, Edinburgh Napier University, [redacted]
	Nominated by: Company
	DOI: NONE
Expert #5	Matt Reed, Consultant, NRS Clinician and RCEM Professor of Emergency Medicine, NHS Lothian, [redacted]
	Nominated by: Company
	DOI- YES Direct - financial The Emergency Medicine Research Group Edinburgh has received sponsorship for the EMERGE10 conference in 2018 from various companies including Medtronic Inc, AliveCor and iRhythm Technologies. 2018 2018 Non-financial professional MR has been supplied with Zio XT monitors and ECG analysis services free of charge for research purposes from iRhythm Technologies between 2015 and 2017. MR has received funds for consultation from Medtronic Inc in 2018 and 2019. 2015 2019

	Non-financial professional MR is supported by an NHS Research Scotland Career Researcher Clinician award. 2012 To date
Expert #6	Dr Ruth Chambers, Clinical lead for technology enabled care programme, Staffordshire Sustainability & Transformation Partnership c/o employment by Stoke-on-Trent CCG, [redacted]
	Nominated by: Company
	DOI: NONE
Expert #7	Shona Holding, Cardiovascular advanced nurse practitioner, Affinity care, [redacted]
	Nominated by:company
	DOI: NONE
Expert #8	Dr Shouvik Haldar, Consultant Cardiologist & Electrophysiologist, Royal Brompton & Harefield Hospitals, [redacted]
	Nominated by: company
	DOI: NONE

	Questions		
1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	Expert #1: Have used Kardia mobile for several years now. We search for symptomatic arrhythmias including AF, SVT, VT etc Yes as above	
	Have you used it or are you currently using it?	Yes frequently	
	Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	I hear lots of people using them	
	Is this procedure/technology performed/used by clinicians in specialities other than your own?	We specifically preclude other specialities from using them other than cardiology although are about to do a trial will post stroke patients to look for AF	

	– If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	no	
		Expert #2 I have been using KardiaMobile since the autumn of 2017. We have 60 devices in our trust which we loan out to patients for 2 months at a time, or shorter if we obtain symptom correlation. We use it in our arrhythmia service to identify arrhythmias in patients with symptomatic palpitations. We have developed a standard operating procedure for its use and provide patients with detailed instructions on how to use it, based on the company's own literature. We encourage patients to email us ECG rhythm strips recorded on their KardiaMobile device when they are symptomatic with palpitations. The email is checked every two days and I run an Alivecor clinic on Friday where I telephone patients to discuss results of their ECG rhythm strips. Currently using I know of several other NHS centres who use it. Some in a similar way to us and some who use it for identification of silent AF both in primary and secondary care. The innovation agency in north west England had a "detect, protect, perfect" program a couple of years ago where they were lending devices to GP's, the uptake however was slow. Yes stroke specialists use it.	

		I occasionally use KardiaMobile rhythm strips to refer patients for EP studies and ablation procedures if it's all we have	
		Expert #3 I have been using these devices for some time and continue to do so. They are widely used in the NHS, particularly in Primary care and have been issued to Primary care in large numbers by the Academic Health Science Networks (AHSN)	
	–	Expert #4 I am very familiar with the technology, having undertaken the first validation study in humans, and the first screening study in community pharmacies. The protocol for this study was then used in numerous studies globally, including in Scotland, where it has been demonstrated that detection of AF rates were significantly elevated, and that patients who were detected had high risk of future stroke. Please note my expertise relates to atrial fibrillation detection, and not to the use of the new Kardia 6L. However, I see this technology as an advantage as it adds to the range of conditions that could potentially be detected. One of the previous challenges with scaleability was the number of 'unknown' diagnoses (roughly 10%) but improved algorithms for detection of sinus tachycardia/ sinus bradycardia, etc should reduce this burden. In Scotland, uptake has been patchy and dependent on local champions. Recommendation	

		of it's use for clinical purposes should increase uptake, particularly if it is added to national procurement lists A range of clinicians have successfully used this technology including nurses, cardiologists, pharmacists, podiatrists and general practitioners. In a recent qualitative study we have done, as part of a Horizon 2020 funded study 'digital risk reduction in atrial fibrillation in Europe', participants highlighted other opportunities for detection such as dentistry. Because of the ease of use, it could be used for self-screening. This is currently being investigated in research studies. A key challenge is ensuring that once AF is identified it is appropriately managed. We have worked on projects embedding this technology in general practice coupled with electronic decision support tools.	
	–	Expert #5 I have extensive experience of Kardia/AliveCor both through clinical research (IPED study; see below) and introducing the Kardia technology into clinical care through the establishment of our Smartphone palpitation and pre-syncope ambulatory care Clinic (SPACC) service. All patients aged 16 years or older presenting to the Emergency Department (ED) or Acute Medicine Unit (AMU) of the Royal Infirmary of Edinburgh (RIE) with palpitations or pre-syncope, whose ECG is normal, who have a compatible Apple/android phone, tablet, or watch, and in whom an underlying cardiac dysrhythmia is possible, are offered an appointment at the	

		SPACC, which was based in an ambulatory care clinic setting beside the ED. Further details of the service available at https://www.mdpi.com/1010-660X/57/2/147 Emergency Department/ AMU RIE, Smartphone Palpitation Service SOP: Available online: https://www.emergeresearch.org/wp-content/uploads/2015/12/Palpitation-Ambulatory-care-pathway-v3-13-07-2020-FULL-VERSION.pdf (accessed 6 February 2021). The technology is used widely on an ad hoc basis (and in some centres as part of a more organised care pathway) in cardiology clinics but less so in other settings. Being available to the public via Amazon, it is something increasingly that patients are purchasing and attending with symptomatic rhythms to the ED (similarly with the Series 4 Apple watch).	
	–	Expert #6 I have been responsible for writing a 'How to use AliveCor KardiaMobile device' guide for clinicians with a medical student Dr John Marszal – in 2017 -0 for general practice clinicians. I have organised & chaired 4 educational workshops for GPs & nurses across Staffs to learn about best practice in clinical management of AF & use of AliveCor KardiaMobile for AF screening in frontline primary care; 2018-2020. As a result, we have deployed 400 AliveCor KM lead 1s across 113 Staffs practices (I wrote bids for	

		funds successfully from NHSE Estates & Technology Transformation Fund on behalf of Staffs CCGs.) + 10 AliveCor lead 6s. Recently published article with junior doctor describing usage in one of the 6 Staffs CCGs. We advise that practice nurses screen patients whom they are reviewing for long-term conditions cae eg annual review who are not known to have AF - for AF with AliveCor devices; or opportunistically at practice 'flu clinics. We have also produced webinars for practice teams to emphasise potential of digital aids for cardiovascular conditions – for screening & clinical managements – this included demonstrations of use of AliveCor KM for clinicians by clinicians; and patients' own perspectives. The webinars were watched by circa 300 clinicians & were well evaluated (September 2020-January 2021) I do not know if secondary care & community care clinicians use AliveCor in these ways. I stopped practising as a GP in 2017- so I do not screen for AF on frontline myself. Some of the CCGs' workshops were supported by	

	–	Expert #7 I have extensive experience of using kardia. Have used it in my daily practice for 5 years. Yes Yes but less, often as currently using a different device I have been involved in auditing data of a palpitations pathway using kardia. Not sure but aware some centres are setting up palpitations pathway using kardia. Some GPs may use them for screening ..use if pick up an irregular pulse I work within a community cardiology service. I have been involved in auditing data of a palpitations pathway using kardia.	
	–	Expert #8 I am very familiar with the technology. I have the device which I use to show patients in clinic. I recommend the device to patients to buy if we are embarking on a journey to capture arrythmias I am not involved in research using it.	

		It is being increasingly recommended especially by EP cardiologists but there is significant geographical variation in popularity. It is being increasingly used but overall penetrance is small. The speed of uptake is going to be fast particularly if patients purchase themselves. Yes – sometimes neurology when dealing with cryptogenic stroke. N/A as I am cardiologist.	
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have done bibliographic research on this procedure. no I have done research on this procedure in laboratory settings (e.g. device-related research). no I have done clinical research on this procedure involving patients or healthy volunteers. We have published an poster in HRC I have published this research. As above	
		Expert #2 I have done bibliographic research on this procedure. Yes I have done research on this procedure in laboratory settings (eg. device-related research). No	

		I have done clinical research on this procedure involving patients or healthy volunteers. Yes I have published this research. Yes I have had no involvement in research on this procedure. n/a I published a poster presentation for the Heart Rhythm Congress on how we use the device and results to date.	
		Expert #3 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure. Other (please comment)). I have not been involved in research or development of this device.	
	–	Expert #4	

		I have done bibliographic research on this procedure I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research.	
	–	Expert #5 I have done clinical research involving patients. I was the Chief Investigator (CI) of the Investigation of Palpitations in the ED (IPED) study: Reed MJ, Grubb NR, Lang CC, O'Brien R, Simpson K, Padarenga M, Grant A, Tuck S, Keating L, Coffey F, Jones L, Harris T, Lloyd G, Gagg J, Smith JE, Coats T. Multi-centre randomised controlled trial of a smartphone-based event recorder alongside standard care versus standard care for patients presenting to the Emergency Department with palpitations and pre-syncope: the IPED (Investigation of Palpitations in the ED) study. Lancet eClinical Medicine 2019; 8: 37–46; PMID: 31193636 DOI: 10.1016/j.eclinm.2019.02.005 This showed that the Kardia smartphone-based event recorder increased the number of patients in whom an electrocardiogram (ECG) was captured during symptoms over five-fold to more than 55% at 90 days compared to standard care and concluded that this safe, non-invasive and easy-to-use device should be considered part of	

		on-going care to all patients presenting acutely to ED or acute medicine with unexplained palpitations or pre-syncope. I am also CI on the implementation study published in Medicina: Reed MJ, Muir A, Cullen J, Murphy R, Pollard V, Zangana G, Krupej S, Askham S, Holdsworth P, Davies L. Establising a smartphone ambulatory ECG service for patient presenting to the Emergency Department with pre-syncope and palpitations. Medicina https://www.mdpi.com/1010-660X/57/2/147	
	–	Expert #6 I have not done bibliographic research on this procedure; instead I have done service redesign – as described above; overseeing clinicians' education/confidence/competence to use this procedure on their patients in their own workplace settings. I have published this as service redesign – not research – as above Mathew S and Chambers R. Improving the utility and sustainability of novel health technology to improve clinical outcomes for patients: an East Staffordshire experience of screening for atrial fibrillation with the AliveCor KardiaMobile. BJGP Open February 2021. DOI: 10.3399/BJGPO.2020.0169 https://doi.org/10.3399/BJGPO.2020.0169	

	–	Expert #7 I have had no involvement in research on this procedure.	
	–	Expert #8 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure. Other (please comment)	
	Has the technology been superseded or replaced? (MIB question)	Expert 1 -not asked	
	–	Expert 2-not asked	
	–	Expert 3; This particular device (Lead 1 ECG) has been superseded by an updated device that does a 6 lead ECG but the lead 1 is cheaper and still holds its place.	

	–	Expert 4-not asked	
	–	Expert 5-not asked	
	–	Expert 6-not asked	
	–	Expert 7: Other devices are available such as zenicor which are an alternative . don't think it has replaced kardia	
	–	Expert 8: No – not at present despite the proliferation of smartwatches particularly apple watch 4 which has the ECG recording capability but it is x4 times more expensive.	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: As we have bene using it for some time it is now an integral part of our practice and is much better than our old cardiocall event recorders and much cheaper Established practice and no longer new. In my view yes	
		Expert #2 It was innovative in 2017, it has become well established now and because the device can be used within the patients home it is excellent for identifying ECG changes in patients with symptomatic palpitations. It can also be used for the opportunistic detection of AF and is more reliable than pulse checks in general practice. The major advantage of the device is that it is free to download the application software and the device itself is inexpensive. Established practice and no longer new. no A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. no Definitely novel and of uncertain safety and efficacy. no The first in a new class of procedure. yes	
		Expert #3 I would say that this particular device is innovative. The gold standard for AF diagnosis is	

		a 12 lead ECG. Feeling the pulse manually or some other wearable technology give an indication of if a pulse is irregular. This falls in between and gives a strong indication if the user has Atrial Fibrillation (AF). Established practice and no longer new. Yes, A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	
		Expert #4 This technology has been widely tested over the last 10 years and the data suggest high level of diagnostic accuracy. Use of single-lead ECGs in the European Society Guidelines is a class 1 recommendation, and much of the evidence for this has been developed using KardiaMobile technology A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	
		Expert #5	

		In my opinion use of the AliveCor/Kardi is becoming increasingly used in clinical practice in Cardiology services. Use in an ED and acute medicine service is definitely novel. I would say it is 'Definitely novel but has increasing evidence of safety and efficacy'	
		Expert #6 Established practice and no longer new.	
		Expert #7 Use of kardia is innovative and a novel concept , associated with an increased diagnostic yield as used during symptoms and immediately following detection of an irregular pulse Established practice and no longer new.	
		Expert #8 It is a novel concept as it gives the patient the power to control their data. Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy.	

		The first in a new class of procedure.	
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: Both replace and additional	
		Expert #2 We have been using it to replace ambulatory monitoring in arrhythmia detection, in this respect it can definitely replace standard care in some cases although the trace quality with ambulatory monitoring is of a better quality. Ambulatory monitoring is restricted by time and cost, this is a value for money alternative.	
		Expert #3 This replaces feeling pulses in some scenarios and is an additional technology in others.	
		Expert #4 This would depend on recommendations from NICE. ESC recommends that diagnosis of AF can be made on a single-lead ECG without need for confirmatory 12-lead ECG. If we accept this is a valid technology, then it could reduce the need for 12-lead ECGs which require more time to take, need a dedicated space, and need specialist interpretation.	
		Expert #5 Definitely has the potential to replace the 24hr Holter from its position as current standard care.	
		Expert #6 It is part of usual service in majority of practice teams that have at least one AliveCor KM device- across Staffordshire general practices	

		Expert #7 It will replace need for 24hour or prolonged holter monitoring in most cases. But may be used in addition to prolonged monitoring	
		Expert #8 It is very innovative and novel but overall likely to be in addition to standard care. In some instances, has the potential to change standard of care for investigating arrhythmias	
	Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing? (MB question)	Expert 1-not asked	
		Expert 2-not asked	
		Expert 3: There are many similar technologies on and entering the marketplace for AF detection, far too many to list. They have varying modes of operation and varying methods of detecting AF with variable accuracy and reliability. This device has high degree of specificity and sensitivity and connects to a smart phone or tablet to give a nice visual of the ECG that can be easily transmitted by e-mail. It also gives an excellent estimation of heart rate based on a multiplication of a 30 second ECG. Other devices will have some of these functions.	
		Expert 4-not asked	

		Expert 5-not asked	
		Expert 6- not asked	
		Expert 7: Smart watch: produces very clear ECG trace but is not NICE approved. Zenicor produces lead I trace. No mob phone is needed, easy to use, device is size of a mob phone so is also portable. unable to see ECG during recording. The ECG is sent to a database. Patient details have to be entered to database before use. Produces clear tracings most of the time. Has callipers so can measure intervals more accurately	
		Expert 8: No – not that perform as well as this device which also has a favourable cost profile.	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Our previous event recorder was a cardiocall which is an old device and quire cumbersome	
		Expert #2 Currently ambulatory monitoring is widely used for arrhythmia detection in symptomatic patients, problems occur when patients do not have symptoms over the period of time the monitor is in place.	
		Expert #3 Opportunistic manual palpation of pulses to look for undetected AF.	

		Expert #4 For diagnosis of AF, 12-lead ECG is currently required, although single lead ECG is considered acceptable in ESC guidelines	
		Expert #5 Repeated unrewarding 24hr Holter monitors. Although increasingly AliveCor/Kardia is being used in clinical practice in Cardiology services (although without much research evidence for its safety and efficacy). Use in an ED and acute medicine service is more novel.	
		Expert #6 Ad hoc feeling of a patient's pulse to detect AF by a clinician. If concerned might be AF maybe arrange a 12 lead ECG or holter to be worn from 2-14 days; but not every general practice has an ECG machine or expert clinician to interpret the tracings. Most practices would need to refer patient for wearing a holter (costly procedure); whereas AliveCor KM device can be used there & then; or purchased by patient who can save tracings to show clinician.	
		Expert #7 Prolonged monitoring but in some arrhythmia centres, lead 1 device is used to monitor intermittent symptoms	
		Expert #8 When investigating arrythmias – 24-72 holter or 7 day holter in first instance.	

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: We also used Diagnsticks which is similar but only for patient who do not have or can not use a mobile phone as they are much more expensive.	
		Expert #2 Yes We also “Mydiagnostick” devices in place of KardiaMobile for patients without a smartphone/tablet or who are not confident using the Kardia/Mobile device due to technological or dexterity issues. KardiaMobile is also not recommended for paediatric patients and so we use Mydiagnostick to identify arrhythmias in paediatric patients.	
		Expert #3 There are many similar technologies on and entering the marketplace for AF detection, far too many to list. They have varying modes of operation and varying methods of detecting AF with variable accuracy and reliability. This device has high degree of specificity and sensitivity and connects to a smart phone or tablet to give a nice visual of the ECG that can be easily transmitted by e-mail. It also gives an excellent estimation of heart rate based on a multiplication of a 30 second ECG. Other devices will have some of these functions.	
		Expert #4 There are a range of single lead ECGs on the market, some which are personally activated, eg Withings watch, Apple watch, Fitbits. There are also Zenicor, MyDiagnostick, and other single lead patch technologies, eg Bardy Patch, QardioCor, and ECG 24. KardiaMobile is different	

		in having 6-lead ECG capability, and validated algorithms for detection of more than just AF.	
		Expert #5 Continuous ambulatory ECG monitors are available (e.g. BG mini from Preventive and Zio from iRhythm) but are more expensive and are only able to record continuously for 14 days meaning that if the patient's palpitations are less frequent they may not be detected. Investigation of palpitations does not require a continuously recording device as unlike syncope (blackout), patients are conscious when they have their episode and are therefore able to use an event recorder such as the Kardia/AliveCor. Other more traditional event recording devices are also on the market but not linked to smartphones. Other smartphone based pulse rate devices are also available such as through Samsung, and other healthcare companies (e.g. Preventicus Heartbearts) but do not record an ECG tracing, only a pulse rate through the phone camera.	
		Expert #6 I'm aware that the Apple watch has facility to record heart tracing via pulse rate; and some sphygmomanometers do. But I don't know how reliable they are. Same for fibricheck device- am not familiar with it & don't know how reliable it is.	
		Expert #7 Smart watch: produces very clear ECG trace but is not NICE approved. Zenicor produces lead I trace. No mob phone is needed, easy to use, device is size of a mob	

		phone so is also portable. unable to see ECG during recording. The ECG is sent to a database. Patient details have to be entered to database before use. Produces clear tracings most of the time. Has callipers so can measure intervals more accurately	
		Expert #8 No – not that perform as well as this device which also has a favourable cost profile.	
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Easy to use, cheap, widely available, can send results over the internet, we can buy lots of them so can expand the service.	
		Expert #2 Patients are able to record a single lead ECG trace when they are symptomatic with palpitations, this can then rule in or rule out an arrhythmogenic cause for their symptoms if they are able to record a trace at the exact time of experiencing symptoms. Arrhythmias can now be diagnosed that previously were not captured on any kind of ECG monitoring. Patients can also use the device to detect asymptomatic AF if it is suspected.	
		Expert #3 AF causes blood clots and strokes. This technology aids AF detection. When AF is detected medication can be given to prevent strokes. AF is more common with advancing age and as the average age of the population	

		increased, AF is becoming more common world-wide.	
		Expert #4 Rapid detection and early implementation of management plans that could potentially prevent stroke. In our work with patients in the use of this technology, patients who have not got a diagnosis are generally interested in the tech, but not worried about it, and those who have been diagnosed are relieved and grateful to have AF detected	
		Expert #5 Easy to use and distribute from hospital and community health settings. Relatively inexpensive. Reusable Increased efficacy in detecting symptom rhythm correlation. Also a 'negative' finding of sinus rhythm/sinus tachycardia or ectopic beats during symptoms is as valuable as detection of a cardiac dysrhythmia as this will allow reassurance that the patient does not have a cardiac dysrhythmia as the cause of their palpitations.	
		Expert #6 Easy to use, quick (30 seconds), likely to detect AF if patient has irregular heart rate during the test.	
		Expert #7	

		Using this technology means heart rhythm can be captured during symptoms… often 24 hour holters miss symptomatic episodes	
		Expert #8 Quicker time to (accurate) diagnosis for investigating arrythmias / following up for recurrence post AF management (DCCV or catheter ablation). User friendly Patient orientated and patient in control of recording symptoms and capturing data which should give excellent symptom – rhythm correlation.	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Symptomatic patients Asymptomatic patients who need to change therapies based on +ve findings ie AF post stroke or TIA	
		Expert #2 Yes, patients with symptomatic palpitations and stroke patients in who we may suspect AF but it has not been proven.	
		Expert #3 As it needs to be linked to a smartphone or tablet, there is the potential for digital exclusion. AF is far more common in advancing age and so is digital exclusion so the younger AF patients would benefit more in personal use. When used	

		for AF detection by health care professionals this evens out.	
		Expert #4 Our multicountry patient-level meta-analysis of 141,220 screened individuals suggest that the cost benefit is adults over 65 years. The benefit grows with increasing age and stroke risk	
		Expert #5 1) Patients with palpitations to detect atrial fibrillation, atrial flutter and SVT. 2) Stroke; CVA/TIA patients to detect asymptomatic paroxysmal atrial fibrillation Asymptomatic patients to detect asymptomatic paroxysmal atrial fibrillation allowing treatment with anticoagulation where appropriate and reducing stroke/TIA primary occurrence.	
		Expert #6 Those with comorbidities, aged>60 for whom atrial fibrillation is more likely than younger/healthier people.	
		Expert #7 Those with intermittent palpitations lasting longer than 30 seconds. Those who have irregular pulse detected.	
		Expert #8 Most would benefit. Only those who were particularly elderly of had medical problems	

		such as severe rheumatoid arthritis may find it challenging to use.	
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: Yes undoubtedly it already has in our organisation	
		Expert #2 Yes, it can reduce the number of ambulatory monitors used both in primary and secondary care. This could lead to less hospital visits and a shorter wait for diagnosis. Patients are also able to buy their own device. We have a dedicated email address so that patients can send in ECG traces for diagnosis. If they have tried KardiaMobile with us and not had any symptomatic episodes they are able to buy their own device and continue to send in any symptomatic traces.	
		Expert #3 I am just starting a pilot to issue my patients with these devices for a 6 month trial. A satisfaction survey will help us understand if the patients felt it helped with fewer hospital/GP visits in managing their condition. When used in screening programmes (as I and others have done previously) it has led to AF detection and stroke prevention medication issue.	
		Expert #4 Yes, this could reduce the number of visits to hospitals, especially in areas with limited access to ECGs. In rural and remote settings, the technology could be posted to patients. Because the data is cloud based it could be viewed at a hub, and recommendations	

		for treatment could be implemented without the need for patients to travel. It is considered highly likely that early detection of AF will prevent stroke, although prospective studies are ongoing. Screen-detected AF patients generally have high risk for stroke and warrant anticoagulation.	
		Expert #5 Definitely. Will allow earlier pick (or ruling out) of atrial fibrillation, atrial flutter and SVT in patients with palpitations. Reduced fruitless investigation. Better detection of asymptomatic paroxysmal atrial fibrillation in stroke/TIA patients allowing treatment with anticoagulation where appropriate and reducing stroke/TIA recurrence.	
		Expert #6 Main benefit is increased diagnostic rate for AF, then clinician starts anticoagulation treatment if justified by score; and a stroke is potentially avoided- saving hospital admission/death/loss of job & increased social care costs. Thus improved clinical & social outcomes/saved NHS costs, esp as a stroke resulting from AF is often more serious/disabilitating than stroke from non-AF cause. It would not change current pathway- just underpin in.	
		Expert #7 Yes, virtual palpitations pathways are being set up..	

		Patient history taken from referral and /or over the phone. Patient set up with device for a set period (1-3 months). ECG traces sent are interpreted by a Designated HCP qualified in ECG interpretation. Review is arranged once traces received and interpreted. Review often done by phone. This has reduced clinic attendances and reduced need to attend for holter fittings thus reducing footfall and social contact	
		Expert #8 Yes – absolutely on all those counts. Hence why I recommend usage of this device to my patients.	
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: Cost lest per item but as we use lots of them it does cost more overall given more devices and clinical physiology/ arrhythmia nurse time spend dealing with results. However it is expanding to meet the demands of the service.	
		Expert #2 It will cost less in capital terms, each device is currently £82.50 (plus VAT) compared to the price of an ambulatory monitor (circa over £1000). Staff still need to check incoming traces via email, this is currently completed by clinical investigations staff or arrhythmia nurses. This can be done from any care setting, including working from home. Due to COVID restrictions on outpatient activity more and more outpatient activity will be completed remotely. Sending patients kardiamobile through the post or to be picked up locally in rural communities could offer significant health economy savings.	

		Expert #3 It is likely to save significant overall cost. Preventing 1 stroke saves thousands of pounds in the first year of care and subsequent years if the patient survives.	
		Expert #4 This would reduce time (KardiaMoblie is handheld, or for six-lead, both hands and one knee) and only takes 30 seconds to record. It does not require the patient to undress, or for multiple leads to be attached. It does not require much training to use, and patients have successfully used it to self-screen. The cost of a single KardiaMobile is significantly less than the purchase of a 12-lead ECG machine	
		Expert #5 Likely to cost less than current standard care. No associated ECG reporting costs. Device no more expensive that current standard care devices.	
		Expert #6 An AliveCor KM device costs around £90 (lead 1) and can be used for many patients. Takes about 5 mins for a nurse or doctor to learn to use it. This is in addition to standard care – but with savings to come in avoiding a patient having a stroke/associated home visits etc. Then the cost of confirmatory 12 lead ECG – usual service.	

		Expert #7 I expect it will be cost neutral or cost less as this technology will provide a rhythm strip during symptoms so even if ECG is normal patient can be reassured their symptoms are not caused by a dysrhythmia. This will reduce number of repeat holters and recurring referrals	
		Expert #8 Far less Patients - Earlier diagnosis, quicker intervention and hence better patient outcomes. Hospital – Earlier diagnosis, less repeated investigations, fewer hospital visits, ability to fit in with remote consultations and better patients outcomes and satisfaction.	
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: Same answer as above	
		Expert #2 We are currently researching this very question. We are comparing the diagnostic yield of kardiamobile compared to ambulatory monitoring. My feeling is that Kardiamobile will be a cheaper and more flexible alternative.	
		Expert #3 In the majority of cases it is being used as a screening tool. The resource impact is negative in purchasing the devices. Positive impact on resource is found all across the healthcare economy in paying for and treating fewer strokes. More AF detection will mean more 12	

		lead ECGs required and purchase of more stroke protection medication but models show that stroke protection medication demands considerably less resource that stroke treatment.	
		Expert #4 This is a difficult question, as it could increase diagnosis of AF, which would be more costly in terms of increased prescription of NOACS. On the other hand, all modelled cost-effectiveness studies suggest this will be cost-effective and in some scenarios cost-saving.	
		Expert #5 Likely to cost less than current standard care	
		Expert #6 As above	
		Expert #7 The staff resource should not change, those who interpreted holters can be assigned to Lead I interpretation. A palpitations service can be run from hospital out-patient setting or a community cardiology service	
		Expert #8 Less	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: Ensure there is a secure upload site, email currently for us	

		Expert #2 Clinical staff need to oversee interpretation of ECG traces. The devices automated software for identifying AF for instance is not accurate enough to be reliable. Clinical physiologists or nurses are the best and most cost-effective members of staff to be performing the ECG interpretation. Staff with a good understanding of smartphone/tablet technology are also required to explain to the patient how to use KardiaMobile effectively.	
		Expert #3 The technology is fairly easy to use for healthcare professionals and has no implications on infrastructure. No training is required. It can be difficult for patients to use if not familiar with digital technology/smartphone/tablet use.	
		Expert #4 This requires less clinical facilities as there is no requirement for special rooms to take ECG, and can be done quickly and easily, reducing need for space to take 12-lead ECGs	
		Expert #5 Healthcare staff education required to instruct patients how to use device. NHS wifi needs to be suitable to allow app set up in hospital setting. There is the option to have a Kardia/AliveCor dashboard placed onto your hospital IT system	

		to allow recorded patients ECGs to be viewed remotely. There are some IT challenges here. Data protection consideration with patients putting their identifiable information into the Kardia/AliveCor app. Kardia/AliveCor app also offers patient the opportunity to have ECGs reported by a cardiologist for a fee which would not be required with an NHS adoption model and would therefore need to be removed or turned off.	
		Expert #6 As above- just minor addition to usual care – no extra facilities needed – unless clinician wants a standalone phone to receive patients' heart tracings.	
		Expert #7 Can be readily used in a cardiology team…. need admin and HCA to set patient up with device and HCP trained in ECG interpretation Dr, arrhythmia nurse, cardia physiologist.	
		Expert #8 Need infrastructure for data collection and data interpretation	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: Yes but not very complex nor time consuming for those used to looking at ECGs/ arrhythmias	
		Expert #2 A level of competent ECG interpretation is required. We use staff that have completed a	

		healthcare science degree or nurses who have completed an ECG course run by the Society for Cardiological Science and Technology.	
		Expert #3 No, just a little practice.	
		Expert #4 Minimal training is required. The technology has been used successfully by a range of healthcare disciplines and by patients	
		Expert #5 Some simple training is required to educate patients and healthcare staff how to use device/app, and if required the Kardia/AliveCor dashboard.	
		Expert #6 5 mins on average- but in Staffs covered this in a best practice clinical update workshop; or in webinar demonstrating it from clinician & patient perspectives.	
		Expert #7 Infection control.. devices should be cleaned between use, Confidentiality issues…. If using personal phone to use kardia , eg when pt is in clinic.. ECG should NOT be ID'd. ECG without patient details should be emailed directly to own email and then attached to the notes at time of recording. The ECG can then be identified once attached to the notes.	

		Expert #8 Yes – to analyse single lead ECGs	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: If patients can not use the device then we get no or poor quality recordings	
		Expert #2 Improper diagnosis of ECG traces is the main problem and particularly if atrial fibrillation is diagnosed from the device software without clinical input from someone with ECG interpretation knowledge. Patients have been anticoagulated inappropriately and not anticoagulated appropriately on the basis of KardiaMobile recordings although this is rare. Several, the problem of incorrect diagnosis is discussed here: Mobile Health, Solution or Threat, Neth Heart J (2019) 27:16–17. Several examples of incorrect diagnosis of AF by clinicians relying on computer generated algorithms. Indication of a “normal” reading when actually an arrhythmia exists eg. Slow flutter	
		Expert #3 I am not aware of any adverse events or risks.	

		Expert #4 The technology presents no risk of harm when used appropriately. As with any reusable product there is a risk of cross-contamination if the device is not cleaned properly I am not aware of any adverse events There is a potential risk of false negatives and false positives, resulting in over- or under-diagnosis but the algorithms are highly sensitive and specific, so this risk is low. I cannot think of any theoretical adverse events that could occur	
		Expert #5 No known adverse risks.	
		Expert #6 From memory specificity & sensitivity rates are circa 96%. Thus potential harms are one in 25 chance of false reassurance. And for paroxysmal AF, patient may be reassured falsely if told heart rate normal with AliveCor screening & clinician does not describe that their AF may be on/off Nil adverse events observed,	
		Expert #7	

		Infection control…all devices cleaned between use. Identity of patient… ensure no one else has used it eg a child/relative Confidentiality issues when sending tracings and when stored on patient's notes.	
		Expert #8 False positive if data not analysed by appropriate personnel. But if clarification of ECG required patient can always have standard care investigations – this will be fairly rare in occurrence	
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Can easily record and ECG when required	
		Expert #2 Ability to diagnose a range of arrhythmias using skilled clinician ECG interpretation	
		Expert #3 More cases of AF are being detected and more stroke prevention medication is being given.	
		Expert #4 Detection of abnormal heart rhythms in Lead I (Kardia single-lead) and Leads I, II, III, aVL, aVR, aVF (Kardia 6-lead)	
		Expert #5 Speed of diagnosis. A 'negative' finding of sinus rhythm/sinus tachycardia or ectopic beats during symptoms is as valuable as detection of a	

		cardiac dysrhythmia as this will allow reassurance that the patient does not have a cardiac dysrhythmia as the cause of their palpitations. Reduction in investigations such as use of repeated unrewarding 24hr Holter monitors Reduction in healthcare usage for repeated attendances with undiagnosed palpitations as diagnosis made.	
		Expert #6 AF diagnosis confirmed by 12 lead ECG	
		Expert #7	
		Expert #8 Patients - Earlier diagnosis, quicker intervention and hence better patient outcomes. Hospital – Earlier diagnosis, less repeated investigations, fewer hospital visits, ability to fit in with remote consultations and better patients outcomes and satisfaction.	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: I have no concerns as long as we get a good quality recording we can make a diagnosis.	
		Expert #2 Clinicians relying on the computer generated potential diagnosis	
		Expert #3	

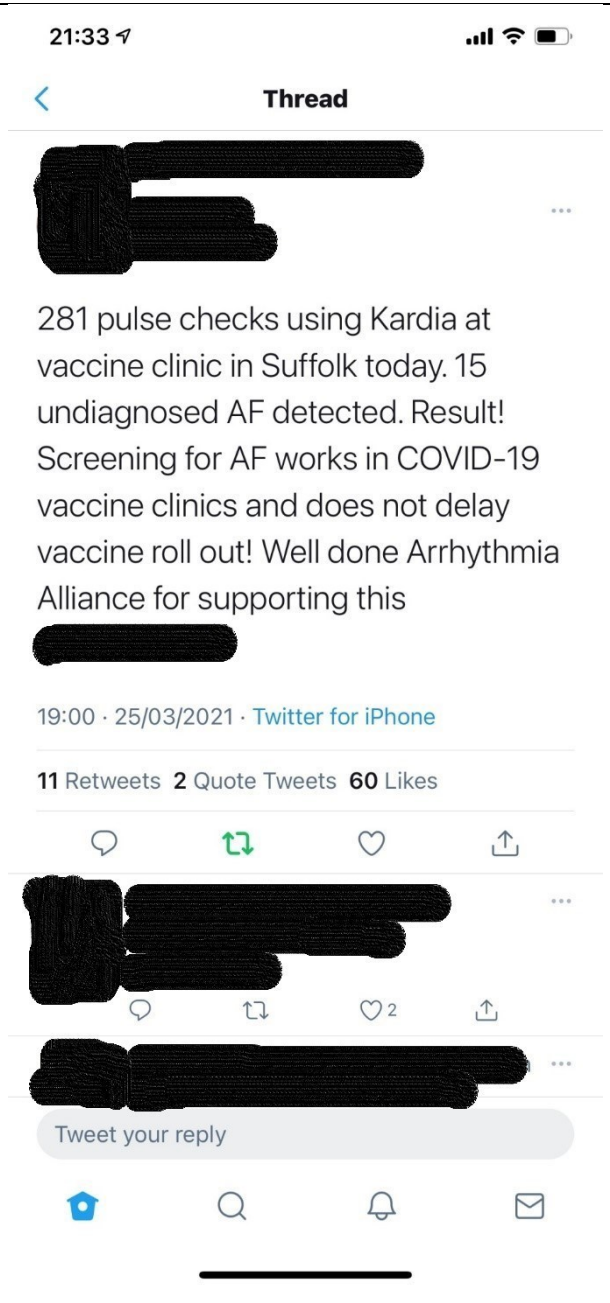
		None.	
		Expert #4 None known	
		Expert #5 IT issues will need some thought e.g. embedding symptomatic/diagnostic ECGs into the Electronic Patient Record, and having the Kardia/AliveCor dashboard placed onto the hospital IT system to allow recorded patients ECGs to be viewed remotely. ECG interpretation can occasionally be problematic when the recorded ECG included noise or artefact. Less experienced clinical staff may have difficulty interpreting the ECG and may be more likely to order additional investigations or further AliveCor wear time, whereas more senior clinicians (and those more comfortable with the technology) in our clinical experience seem to be more comfortable interpreting these recorded ECGs as normal sinus rhythm.	
		Expert #6 The sensitivity & specificity rates- as above	
		Expert #7	
		Expert #8 Nil	
17		Expert #1:	

	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Not in my view	
		Expert #2 Patients with access to smartphone/tablet technology are disadvantaged	
		Expert #3 I am not aware of any.	
		Expert #4 No	
		Expert #5 Whilst the Kardia/AliveCor doesn't seem from studies and our clinical experience to create a population of 'worried well' patients, this needs further work and evaluation. Need to ensure that those recording 'negative' finding of sinus rhythm/sinus tachycardia or ectopic beats during symptoms are reassured and do not continue to use healthcare resources despite the reassuring/benign diagnosis. No evidence of this in our research work but this does need further investigation.	
		Expert #6 Only the sensitivity & specificity rates- as above	
		Expert #7 Maintaining confidentiality when transferring tracing to patient notes and when used on HCP personal phone ; steps can be taken to ensure the patient identity is not exposed or saved on HCP phone. Receive the tracings	

		A secure nhs email is needed	
		Expert #8 Nil	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals. yes	
		Expert #2 Most or all district general hospitals. yes A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #3 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present. Unpredictable.	
		Expert #4 Most or all district general hospitals.- could be scaled anywhere. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK.	

		Expert #5 Most or all district general hospitals. Including community health settings (e.g. GP)	
		Expert #6 Most or all district general hospitals. & other NHS and social care settings	
		Expert #7 A minority of hospitals, but at least 10 in the UK. Will be mainly tertiary centres with arrhythmia service or community cardiology	
		Expert #8 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches.	Expert #1: My arrhythmia nurse David Ferguson has already told you about a poster we submitted	
		Expert #2 Our own service explained via a poster presentation to the 2019 Heart Rhythm Congress: https://www.touchcardio.com/arrhythmia/journal-articles/137-the-introduction-of-a-smartphone-	

	You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	enabled-electrocardiograph-ecg-service-into-an-nhs-arrhythmia-service/ There are several studies looking at measuring QTc interval using the 6 lead version of kardia mobile in COVID 19 patients exposed to multiple QT prolonging drugs	
		Expert #3	


21:33
Thread
[redacted]
281 pulse checks using Kardia at vaccine clinic in Suffolk today. 15 undiagnosed AF detected. Result! Screening for AF works in COVID-19 vaccine clinics and does not delay vaccine roll out! Well done Arrhythmia Alliance for supporting this
[redacted]
19:00 · 25/03/2021 · Twitter for iPhone
11 Retweets 2 Quote Tweets 60 Likes
[redacted]
2
[redacted]
Tweet your reply

		Expert #4 AF Screen international consortium keeps a record of studies published by the group, some of which use Kardia https://www.afscreen.org/	
		Expert #5 Our one year experience of the Smartphone palpitation and pre-syncope ambulatory care Clinic (SPACC) service has been submitted to Annals of Emergency Medicine.	
		Expert #6 Ref cited above And our CVD/digital aids webinars- can send you link if you want	
		Expert #7 Affinity have some raw data on diagnostic yield using alivecor Not published but presented this at Heart Rhythm conference 4-5 years ago.	
		Expert #8	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Don't know	
		Expert #2 Many hospitals and AF detect, protect, perfect projects are publishing the results of their trials	

		Expert #3	
		Expert #4 There are many ongoing studies,. The one we are waiting for is this one- using zenicor, but prospectively tests if screening with a single-lead ECG genuinely reduces strokes https://www.safer.phpc.cam.ac.uk/	
		Expert #5 Not aware	
		Expert #6 Don't know	
		Expert #7 Not aware	
		Expert #8	
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: 80+ % if they have a compatible mobile phone	
		Expert #2 All patients with symptomatic arrhythmias who have access to smartphone/tablet technology. All patients with a diagnosis of stroke with access to smartphone/tablet technology.	

		Expert #3 The UK population is around 65 million. AF is thought to be known in around 1% of the population and undetected in a further 1%. National screening has been considered and narrowly rejected. Opportunistic screening is advocated. Devices like this are likely to help us pick up the potential 650,000 undetected AF cases to prevent many avoidable strokes. (all approximate figures)	
		Expert #4 Adults over 65 years (approx. 11.9 million)	
		Expert #5 Patients with palpitations and pre-syncope commonly present to Emergency Departments, accounting for 300,000 ED presentations a year in the United Kingdom and being one of the commonest presentations to general and family practice (16% of presentations). 1. Thiruganasambandamoorthy, V.; Stiell, I.G.; Wells, G.A.; Vaidyanathan A; Mukarram M; Taljaard, M. Outcomes in Presyncope Patients: A Prospective Cohort Study. Ann. Emerg. Med. 2015, 65, 268–276.e6. 2. Probst, M.A.; Mower, W.R.; Kanzaria, H.K., Hoffman J.R.; Buch E.F.; Sun B.C. Analysis of emergency department visits for palpitations (from the National Hospital Ambulatory Medical Care Survey). Am. J. Cardiol. 2014, 113, 1685–1690.	

		3. Raviele, A.; Giada, F.; Bergfeldt, L.; Blanc, J.J.; Blomstrom-Lundqvist, C.; Mont, L.; Morgan, J.M.; Raatikainen, M.P.; Steinbeck, G.; Viskin, S.; et al. Management of patients with palpitations: A position paper from the European Heart Rhythm Association. Europace 2011, 13, 920–934, doi:10.1093/europace/eur130. I am not aware of the similar primary and secondary stroke and TIA prevention data.	
		Expert #6 10% of adults>60 years?	
		Expert #7 Approx 80% target population	
		Expert #8 50% of target population at least	

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 If they have not got or can not use a mobile phone or tablet then it is no use	
		Expert#2 Yes, users need a degree of computer or smartphone literacy to be able to use the device effectively	
		Expert#3 As it needs to be linked to a smartphone or tablet, there is the potential for digital exclusion. AF is far more common in advancing age and so is digital exclusion so the younger AF patients would benefit more in personal use. When used for AF detection by health care professionals this evens out.	
		Expert #4 Has to be paired with a device- usually a mobile phone. Needs an adequate wifi signal. Problematic if thick walls in the area in which ECG is being recorded.This can be overcome by switching the phone into airplane mode. Difficult if patient has a strong tremor.	
		Expert #5 Covered above	
		Expert #6 Not that I know of	
		Expert #7 Has to be smart phone compatible. Convenience …some say unable to get phone out if working Some of elderly population have poor dexterity	

		Expert #8 How is the device to be funded and if funded by NHS need robust way to ensure the small device is returned to NHS by patient.	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 none	
		Expert#2 Funding considerations are the main barrier and finding time for appropriate analysis of ECG rhythm strips by appropriately qualified staff.	
		Expert#3 No. It is used widely in the NHS.	
		Expert #4 Good linkage of data, concerns about where data is stored and if it is compliant. Needs to be embedded as part of a clear clinical pathway	
		Expert #5 Covered above	
		Expert #6 None known – just getting clinicians thinking they've time to learn to adopt new technology	
		Expert #7 Cost and resource to support its use eg, trained staff to interpret tracings,	
		Expert #8 No	

24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 More data confirming its use and cases identified	
		Expert#2 I think the research base is large enough now for the technology to be used, research as to how much it costs compared to the NHS tariff for ECG monitoring would be interesting.	
		Expert#3 No.	
		Expert #4 As detailed previously, confirmation that early detection of AF prevents stroke is desirable and this evidence is currently being generated	
		Expert #5 Covered above	
		Expert #6 Just good to know latest on sensitivity & specificity rates between AliveCor lead 1s and lead 6s – might already exist.	
		Expert #7	
		Expert #8	

25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#1 Beneficial outcome measures: Numbers of patients with any arrhythmia identified Treatment plans changed as a result of their use Adverse outcome measures: Poor quality recordings that have no use	
		Expert#2 Beneficial outcome measures: Less visits by patients to primary and secondary care premises. Cost of arrhythmia diagnosis compared to ambulatory ECG monitoring Adverse outcome measures: The number of incorrect diagnoses of AF and other arrhythmias	
		Expert#3 Beneficial outcome measures: It would be easy to audit thie device v standard practice to see if there is more AF detection. Adverse outcome measures: Unaware.	

		Expert #4 Beneficial outcome measures: AF detection rates at single time point or over time CHA2DS2VASc scores in identified population % of patients who have an effective treatment plan commenced as a result of detection Adverse outcome measures: N/A	
		Expert #5 Outcome measures: Cost of diagnosis Palpitations: 1) Speed of diagnosis of a clinical symptom/ECG rhythm correlation. 2) Reduction in investigations such as use of repeated 24hr Holter monitors 3) Healthcare usage (e.g. repeated attendances with undiagnosed palpitations/ reduction in investigations) 4) Patient satisfaction measures 5) Reduction in patient anxiety associated with undiagnosed palpitations Primary and secondary AF detection in TIA/CVA patients:	

		1) Reduction in undiagnosed AF 2) Reduction in TIA/CVA rate	
		Expert #6 Beneficial outcome measures: Diagnosed AF/ confirmed by 12 lead ECG Subsequent anticoagulation if AF confirmed. Adverse outcome measures: Someone with paroxysmal AF not detected to have AF when used AliveCor device for 30 seconds; and falsely reassured.	
		Expert #7 Beneficial outcome measures: Suggest over a 6 month period Ease of use for pt Quality of rhythm strip Percentage of sinus rhythm captured Percentage of AF captured Percentage of other dysrhythmia captured Percentage of SR with ectopics. Time scale between receiving device and diagnosis Number of unreadable tracings	

		Adverse outcome measures:	
		Expert #8 Beneficial outcome measures: Time to diagnosis - months Strokes prevented – over 1 year compared with standard care PROMS over 1 year Adverse outcome measures: False positives rate and impact on PROMS Need to resort to standard of care	
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 It is a great device and has allowed many more patients to be investigated and diagnosed or reassured.	
		Expert# 2 I am convinced that the use of kardiamobile together with other lead one ECG monitors is a useful progression in arrhythmia detection. Resources should be steered towards less hospital visits for patients and this together with other technology can help. Primary care need incentives to use it appropriately and costings need to be accurately calculated in comparison to current NHS tariffs.	
		Expert#3 I find them useful and easy to use in the intended manner. I use them regularly for my patients and get useful results	

		Expert #4 I have worked in AF detection for approximately 11 years. I have conducted a number of studies using Kardia single lead ECG to detect AF.	
		Expert #5	
		Expert #6 Should be adopted at scale as usual service in all NHS settings.	
		Expert #7 Effective at capturing dysrhythmia during symptoms and if irregular pulse detected. Education and good user use will enhance quality of trace. Sometimes tracings unreadable Device sometimes stops working ... often requires new battery . can be tricky changing battery We found, many of elderly population didn't have compatible phone and some unable to coordinate its use. When set up correctly and user shown how to gain best trace, this is a very effective tool to capture dysrhythmias. As a HCP, is useful to have this to hand during consultations, if irregular pulse identified	

		Expert #8	
	How useful would NICE guidance on this particular technology be to you or other NHS colleagues? (Mib question)	Expert 1-not asked	
		Expert 2-not asked	
		Expert 3: NICE guidance would be useful to organisations considering the use of this technology. I think, however, the market is expanding too fast and NICE may be better producing a more generalised guide on technology for heart rate/rhythm detection. Much like the guidance from the British and Irish hypertension society on all the many and various blood pressure monitors out there. That way, new devices can be added as they develop.	
		Expert 4-not asked	
		Expert 5-not asked	
		Expert 6-not asked	
		Expert 7: NICE guidance would help role out this innovative practice and promote virtual palpitations clinics	
		Expert 8: Extremely useful as it would give us a firm mandate to use under the NHS.	

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

GID-MT554 KardiaMobile

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	08/04/2021	Initial teleconference with the company, raising EAC queries on company submission of clinical evidence		EAC notes from call: Appendix 2
2.	14/04/2021	Additional written responses to EAC questions received from the Company		Additional information: Appendix 3

3.	14/04/2021	Expert Engagement Meeting		EAC notes from call: Appendix 4
4.	16/04/2021	Collated EAQs received from NICE		Collated EAQs: Appendix 5
5.	16/04/2021	Paper shared by Ruth Chambers in response to notes from Expert Engagement Meeting		I attach article I mentioned that I co-authored on AliveCor deployment in East Staffs: https://bjgpopen.org/content/5/2/BJGPO.2020.0169.
6.	16/04/2021	Comment from Kevin McGibbon in response to notes from Expert Engagement Meeting		It was nice to meet such a knowledgeable group of hardworking experts, pooling experience in this way. The main problem I see is that it takes a lot of time and hard work to produce guidelines that will probably be out of date before they are published. This is the fate of all guidelines to an extent but this particular technology is evolving very quickly. There will soon be another software update, another improvement on the rhythm recognition algorithm and someone will come up with a new indication for use. Competing companies do produce similar devices that may be cheaper and may/may not be as effective. There are many similar devices like Apple and Fitbit and Fibricheck to name a very few. I wonder if you would consider the system employed by the British and Irish hypertensive

				society to guide on the many Blood pressure monitors available? They have all the known makes and models on a grid. As new models or devices or upgrades appear they are assessed and added. The grid gives the price range, home or hospital use, accuracy, if it has irregular rhythm detection, if it has AF detection, if it can measure heart rate in AF etc. If you did similar with all the devices available for monitoring heart rate/rhythm, this will help clinicians and patients a lot more than one guideline for one device. It could be regularly updated rather that starting from scratch with new guidelines constantly required. It could make a lot better use of the clinical experts time and experience as well as the NICE staff experts. Kind regards. Kevin.
7.	20/04/2021	Question to Company re software options	Good morning Sean, Just wondered if I could ask you a broad question regarding the software options please? The clinical submission surrounds the basic Kardia app (freely available). However I am trying to summarise that other optional software is available. So far I have: • KardiaCare: premium user software, which has additional classifications and includes ECG review by a private professional every 90 days	[Two powerpoint presentations were provided by SW for background regarding KardiaStation and KardiaPro; however these were not included in the assessment and therefore are not described here in detail] Response received 22/04/2021 from SW: Hello Kim Apologies for the delay

			• KardiaPro: optional extra for healthcare professionals which allows remote monitoring of Kardia users and generation of reports • KardiaStation: is this another optional extra for healthcare professionals? Can you check my brief descriptions above are correct? And can you possible provide a short summary describing the difference between KardiaPro and KardiaStation please? Again just to stress that I appreciate that none of the above were not formally included in the assessment report, however much like the MIB I am just trying to summarise what is available for users. Many thanks Kim	The below are perfect but if you would like I have provided further detail but your brief summaries are fine. Please see below • KardiaCare: premium user software, which has additional classifications and includes ECG review by a private professional every 90 days • KardiaPro: optional extra for healthcare professionals which allows remote monitoring of Kardia users ECG and Blood Pressure data and generation of reports. KardiaPro is AliveCor's enterprise platform that allows practices to remotely track their patients' hearts using data from KardiaMobile or KardiaMobile 6L. KardiaPro is used by healthcare providers to support clinical decision making and enable remote patient care. Patient ECGs and blood pressure data are transmitted automatically from the Kardia app to a practice's KardiaPro portal, streamlining interpretation with no data overload. Regarding KS KardiaStation: is this another optional extra for healthcare professionals? KardiaStation is a bespoke app specifically for use in a healthcare environment (i.e. under the care of a healthcare professional) to record ECGs from patients in a healthcare clinic including clinician office, pharmacy or other healthcare settings. Utilises KardiaMobile and KardiaMobile 6L to deliver an immediate result for detection of Normal heart rhythm, Atrial Fibrillation, Bradycardia or

				Tachycardia. KardiaPro connects with KardiaMobile and KardiaMobile 6L to enhance patient care and streamline ECG interpretation through remote patient monitoring. Patient ECG data is transmitted automatically from KardiaStatiion app to an institution's KardiaPro portal. Please see an attached presentations also Please let me know if you need anything further Kind regards
8.	23/04/2021	Question to Company re premium options	Morning Sean, Can I ask: a) What proportion of UK users with basic Kardia app, have upgraded to KardiaCare? b) Can you tell me the number of UK healthcare professionals that have KardiaPro? c) Can you tell me the number of UK trusts (I don't need a list) that have KardiaStation? [Just to remind you that all information will go in our correspondence log which will be published online. If you provide any information that is commercial in confidence can you highlight it in yellow - as this will ensure it is redacted before publication]. Many thanks Kim	Thanks for your email and apologies for the delayed response. Unfortunately the data you request is confidential and I have confirmed internally That we will not be disclosing any numbers regarding this. I hope that is ok and apologies we cannot support further.

9.	07/05/2021	Company Engagement Meeting		Notes from the call: Appendix 6
10.	07/05/2021	Information from Company requested from call - complete list of compatible devices		Company provide link to up to date list of compatible devices: https://alivecor.zendesk.com/hc/en-us/articles/1500000449521-
11.	11/05/2021	Company provided written response to questions raised in advance of the Company Engagement meeting		Dear Kim and team As promised please see attached written responses to the questions (Appendix 7). Mehdi and Amir have hopefully addressed all the model related questions and we can hopefully answer anything further on the call on Thursday. If anything specifically has not be answered clearly please can you let us know prior to the call so we can address these straight away on Thursday along with the model overview? Please let us know if you need anything further
12.	12/05/2021	Additional questions on the economic model sent to Company	Evening Sean, As mentioned yesterday, please find attached an additional round of questions regarding the model. I think this will be the last round of questions. Due to the detail included in the questions, written answers would be preferable please. Many thanks Kim	[CEA_KardiaMobile_V3.0_12052021.xlsm attached] Dear Kim In response to the questions and preparation for the call tomorrow please see an updated version of the model V3.0. Amir has confirmed the updates in the comments below.

				This updated version of the model will be the version that Amir and Mehdi will walk through with you and the team tomorrow. We are still working on the written responses to the questions also. Please let me know if you need anything further in preparation for tomorrow. Enjoy your evening. Kind regards Sean Warren Attached please find a new version (V 3.0) of the KardiaMobile. Following our conversation with Kim and her team, we made some changes to increase clarity in the model. In this version: 1. Changes in the “inter calculation” sheet. a. We removed unnecessary data b. Provide labels for various calculations c. We realized a miscalculation in cell C47 and corrected it. d. We provide some adjustments in this sheet to let users run the model with different AF prevalences (as a proxy of different patient populations) 2. Changes in the “method” sheet a. The model structure diagram is updated We think it would be great to submit it to Kim as a new version of the model before our meeting tomorrow. We will explain this version of the model.

				Best regards, Amir
13.	12/05/2021	Additional questions sent to Company		Responses from Company (Appendix 8)
14.	13/05/2021	Additional questions sent to Experts		Collated responses from Experts (Appendix 9)
15.	13/05/2021	Additional meeting with Company to discuss economic model		Notes from call with Company (Appendix 10)
16.	13/05/2021	Query from Company (and additional information requested on call)	Dear Kim Thank you again for your time today. As promised please see attached the KardiaMobile flow chart that we discussed and demonstrated today [**published in the Assessment Report**] Please can you advise on the following - Do we need to officially submit the flow chart for it to be included?	Hi Sean, Just to formally confirm that you do not have to resubmit any documentation. You have already provided the data flow and the new model, so we can document this in our assessment report. Thank you for checking process. Thank you also for the details of your additional expert.

			- Do we need to officially submit the V3 model also for it to be included? If so please let me know how best to do this eg via the portal? Regarding you question of the experts who supported the model. The following experts were included Dr Yassir Javaid GP specialist interest in cardiology NHS Dr David Albert Chief Medical Officer AliveCor Please let us know if you need anything further. Have a great day	
17.	14/05/2021	Additional query from YYW to DF	Dear David Thank you for the clarification. As suggested, do you think if this is reasonable to assume the time between the confirmation of a AF diagnosis and the start of treatment is around 2 or 3 days? Also you mention that you have a kardiaalivecor clinic, do patients send their ECG traces directly to you? Is there any data sharing agreement between individual patients and clinicians? Thank you. Best wishes Yingying	yes 2-3 days is reasonable. patients send their traces to a dedicated shared email address, this is checked mon/wed/fri by the clinical physiologists and any traces indicating an arrhythmia are forwarded to me, if urgent I will phone the patient on the day I receive them to discuss, if non urgent I will phone the patient Friday morning from alivecor clinic to discuss management options. When patients are seen initially and given the alivecor by the clinical physiologists they understand that they "own" their rhythm strips and by emailing them to a shared inbox they consent for them to be viewed by other health professionals and that any relevant ones will be saved in their medical record.

				hope that helps
18.	18/05/2021 (pdf sent) 20/05/2021 (doc version sent)	Clarification from Company regarding description of changes made to model (v3.0)		Appendix 11
19.	19/05/2021	Updated model	Good afternoon Sean, Thank you. Noting the below in the description of updates you provided, can you please amend the model and resend as a new version please (this will ensure we have the most accurate version on file which can be requested during consultation)? Many thanks Kim	[CEA_KardiaMobile_V3.1_19052021.xlsm attachment] Dear Kim Please see attached updated model as requested Please let me know if you need anything further Kind regards Sean Warren
20.	02/06/2021	Additional information following company fact check	Many thanks again for the EAC assessment report, we are just finalising the factual check and as promised will get this to you by end of day today. Can I just check you are happy for me to upload via the portal and email to you to make sure it comes through ok and in word/pdf format? It has also come to our attention that some important details regarding EU data privacy	Appendix 12

			requirements have not been included in our application. Following some of the previous queries regarding data encryption and handling we wanted to add the following as we feel this is extremely important for the public, NICE, EAC and the committee to know. On data encryption and location: *All data in AliveCor is encrypted at rest using AES encryption and in transmission using TLS 1.2. AliveCor uses a distributed cloud storage system to protect against data loss in the event of a natural or other catastrophic incident and localizes European customer data within the EU for greater privacy protections* *On GDPR, data use and transfer:* *AliveCor's entire platform was also built with privacy in mind. Individuals located in the European Economic Area (EEA) have certain rights in respect of their personal information. AliveCor will provide the capabilities to exercise these certain rights to all our worldwide users, including:* *• the right of access to personal data;* *• the right to correct or rectify any inaccurate personal data;* *• the right to restrict or oppose processing of personal data;*	

			• the right to erase personal data; and *• the right to personal data portability.* *We rely on user consent as a lawful basis processing personal data for the following purposes: 1) initial collection of personal data through the Service; and 2) providing users with marketing or promotional communications. Users may opt out of such communications at any time by clicking the "unsubscribe" link found within AliveCor email updates and changing their contact preferences. Despite the Schrems II decision,* ***AliveCor continues to participate in the EU/U.S.- and Swiss/U.S. Privacy Shield programs and is certified through the Department of Commerce regarding the transfer of any personal data from the EU to the United States.*** *AliveCor also complies with all data transfer requirements under Schrems II.* For reference also see attached our consumer fact sheet. If you have any further queries regarding this please let us know	

Appendix 1

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question [redacted]:

Insert

File attachments/additional information from question [redacted]:

Insert

File attachments/additional information from question [redacted]:

Insert

Appendix 2

GID-MT554 KardiaMobile: Company Engagement Meeting
08/04/2021 @ 13:00

Attendees:
NICE: Ying-Ying Wang (YYW), Kim Carter (KC)
EAC: Kim Keltie (KK), Michael Drinnan (MD), Kathryn Fletcher (KF), Emma Belilios (EB)
Company: Sean Warren (SW), Stefan Holzer (SH)
Device Access UK: (consultancy supporting company submission): Michael Branagan-Harris (MBH)
Optimax Access Ltd: Mehdi Javanbakht (MJ)

Agenda

I. Welcome and introduction

NICE, EAC, Company and Device Access UK and Optimax Access Ltd staff introduced. Questions circulated in advance of the meeting were discussed.

ACTION (SW): the Company will provide additional written responses by Friday 16/04/2021.

POST MEETING NOTE - Additional responses received from SW 15/04/2021

II. Discussion: EAC questions

The technology

1) Can you please provide the CE certification for KardiaMobile-1L, KardiaMobile-6L and Kardia app?
   Answer: CE certification and all IFU were submitted to NICE.
   ACTION (YYW): To check company submission and forward CE certification and Kardia app IFU to EAC.

2) Is there any available evidence comparing KardiaMobile-1L to KardiaMobile-6L?
   Are we able to aggregate evidence together for 1L and 6L (or do we keep separate)?
   Answer: As per current ESC guidelines, only a single lead ECG is required to diagnose AF. The KardiaMobile app's automated detection algorithm only uses the information from lead-I to diagnose AF, therefore KardiaMobile-1L and KardiaMobile-6L can be regarded as equivalent in terms of determination of AF. [Additional leads from KardiaMobile-6L take QT measurements, and can be used in the diagnosis of atrial flutter etc but these are not within scope of this guidance].
3) The KardiaMobile-6L can also be used to take a single-lead recording. Is there any available evidence comparing the single lead recording using the KardiaMobile-6L to the KardiaMobile-1L device?
   Answer: addressed above

4) The electrode on the back of the KardiaMobile-6L is placed on the leg. Where on the leg can this be placed (knee and ankle only)?
   Answer: Recommend left leg or ankle. However only reading from lead-I used for diagnosis of AF.
5) For KardiaMobile-6L is there any evidence looking at whether location/position impacts diagnostic accuracy?
   Answer: Addressed above
6) For KardiaMobile-6L is there any evidence looking at whether location/position impacts proportion of "unreadable" outputs?
   Answer: Addressed above. Company qualified some of the terminology: 'Unreadable' means too noisy and probably useless. 'Unclassified' means not fitting any of the categories; a cardiologist should be able to resolve the diagnosis.
7) Significant smoothing of the ECG trace occurs (as indicated by the company YouTube videos). Can you please provide additional technical details regarding the ECG recording? For example filtering applied, any noise reduction algorithms as these may influence subsequent interpretation by a healthcare professional.
   Answer: Hardware filtering (mains filter - filters out 50-60Hz 'noise'), and app filtering (enhanced and original mode). All rhythm strips include information on filtering that has been applied and scale used in the top-right hand corner (similar to rhythm strips being reviewed in a healthcare setting) – so users will be familiar with this.
8) The output of the ECG analysis by the Kardia app (as provided in the IFU submitted by the company) are stated as:
   - Normal
   - Possible AF
   - Bradycardia
   - Tachycardia
   - Unclassified (interference not detected, but cannot be categorised as Normal, Possible AF, Bradycardia or Tachycardia)
   - Unreadable (interference – too noisy)

   However the clinical submission states that "Premature Ventricular Contractions", "Sinus rhythm with Supraventricular Ectopy" and "Sinus rhythm with wide QRS" are also available options. Can you explain?
   Answer: The above categories are identified by the original algorithm ("AIV1") used by the Kardia app. Additional categories have been added to an updated version of the algorithm, "AIV2" – which re-classifies some rhythms previously classified as "Normal" and provides a classification for some rhythms previously "Unclassified"). AIV2 was recently CE marked (on 31/03/2021) and is available via premium access (*i.e.* KardiaCare or KardiaPro which is the remote patient monitoring platform). There is currently no published evidence on the AIV2 algorithm, but the Company have extensive in-house data if needed.
9) Is any advice given to users when a "possible AF", "Bradycardia", "Tachycardia" output is given?
   Answer: There is a disclaimer at the bottom of every reading which states a healthcare professional should be consulted, and that this device is unable to identify blood clot, stroke or MI.
10) What are the Kardia app software version names, and dates when were they released?

Has classification/software output changed with software updates?
Answer: [Clarification from EAC: we only require information on software versions and dates when major changes where applied which impacted categorisation]. Early version of software did not have "Bradycardia" or "Tachycardia" categories available. Over time the "Unclassified" category has been reduced. Company qualified that major new app versions are distributed only after CE marking for the algorithm has been achieved

ACTION (SW): send the EAC a list of the major software changes (including dates).

11) The device is not intended for use in children, what age cut-off is applied? (Minimum age not stated in IFU).
Answer: 18 years. Users cannot sign up for account (for Kardia app) if they are under 18 years of age.
12) KardiaMobile is not intended for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices. However are there any other objective criteria for suitability before the device is used (e.g. tremor, manual dexterity)?
Answer: Not stated in the IFU however manual dexterity and tremor will impact ability to record a stable ECG as the device requires the user to be still for 30 seconds while the reading is taken.
13) Internet access is required to download the Kardia app. The submission states that "Internet access is not needed when taking a reading", and that data are transferred via high-frequency sound waves for KardiaMobile-1L and Bluetooth Low energy for KardiaMobile-6L; which enables users to obtain an outcome (e.g. of "possible AF") without internet. However is it correct that WiFi and/or mobile connection is required if using KardiaCare membership or KardiaPro software?
Answer: Confirmed that internet access is required to download the standard Kardia app, however when set up the user can take a recording and receive an output without internet. Even with KardiaCare and KardiaPro premium options, you can still record and store ECG traces off-line, these will be synched automatically with the Cloud (virtual storage) when internet access resumes.
14) KardiaBand is no longer available therefore do you agree that all evidence relating to this device should be excluded?
Answer: KardiaBand is considered equivalent to KardiaMobile-1L in terms of determination of AF, however it had additional features and was a wearable (therefore different mode of action).
15) GDPR: can you explicitly list what information is transmitted from the device (personal/sensitive)? In what circumstances are these data points transmitted?
Answer: When downloading the Kardia app some personal information is requested (name, password, height, weight, sex, DOB, email address) to create an account. Each time an ECG is recorded the user has the ability to record notes. When results are shown to user and closed, all information is transmitted to the cloud. Personal data and medical data are stored separately. The GDPR button turns off cloud or local storage of the ECG and the notes, among other things (but not the personal details).

ACTION (SW): The company to confirm what data fields are transmitted from the device.

16) Can users opt-out of personal/sensitive data being transmitted?
Are users still able to use the device (and app) without providing personal/sensitive information?
Answer: Users cannot opt out of personal information during download of Kardia App (this is used to create the user account). Users can opt-out of marketing messages as described in the privacy policy. Users can also opt-out of notes added to ECG being sent to the cloud.

ACTION (SH): To share wording of Privacy policy.

17) What does "de-identified personal data" mean in the terms of service?
Answer: SH clarified that data collected within the EU is stored on the cloud (to enable users to access from several devices) however it is not used for research or other R&D purposes, because data from the EU cannot be transferred to the US.

NHS England's Data Protection Policy requires that personal data must be adequate, relevant and limited to what is necessary for the purpose for which they are collected.

Personal account data and diagnostic data are held separately in the cloud for security purposes to protect against data breaches.

ACTION (SW): To check with colleagues what is meant by "de-identified"

18) Considering the terms of service and privacy policy, what is the formal process when a person withdraws their consent for their data being used?
Answer: At the end of the terms of service there is a section on EU rules, how to contact the AliveCor data privacy officer, understand what data are being held on you etc.
19) The IFU state that "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."
However additional annual membership is required for users to have a healthcare professional review their ECG trace (KardiaCare membership).
What specific information accompanies the trace when reviewed by a professional?
Answer: SW clarified that the premium service KardiaCare does not offer review by a healthcare professional. ECG rhythms are over-read by a cardiac physiologist employed by a private company, not an NHS cardiologist. On the ECG the patient name, DOB, time period, date stamp and determination are tagged**.**

Economic model

20) Could you give us any "heads up" information regarding the economic model, in terms of:
    - Software used (Excel, other).
    - Model structure (decision tree, Markov)

    Answer: Excel Markov model.

III. Confidentiality checklist

Further to this introductory meeting, the EAC and the Company can liaise directly (copy in YYW). All communications that inform the Assessment Report will be recorded in the

Correspondence Log by the EAC. The Company are asked to inform the EAC of any commercially sensitive data or data which are shared as Academic in Confidence (text can be highlighted to indicate sensitive information). This information will be fully redacted before the Correspondence Log goes into the public domain.

IV. Next steps

- Expert engagement meeting on 14/04/2021
- Company to send economic submission on 28/04/2021
- Company engagement meeting 07/05/2021
- Final submission by EAC on 27/05/2021

V. AOB

No other business was discussed

Appendix 3

EAC Questions for AliveCor

The technology

1) Can you please provide the CE certification for KardiaMobile-1L, KardiaMobile-6L and Kardia app?

Sent to Ying-Ying Wang and Kim Keltie 13th April including CE certificate and declaration of conformity

2) Is there any available evidence comparing KardiaMobile-1L to KardiaMobile-6L?

NO as discussed KardiaMobile-1L to KardiaMobile-6L, the automated algorithm is derived from lead 1 in both KardiaMobile and KardiaMobile6L which is the same

Are we able to aggregate evidence together for 1L and 6L (or do we keep separate)?

Yes

3) The KardiaMobile-6L can also be used to take a single-lead recording. Is there any available evidence comparing the single lead recording using the KardiaMobile-6L to the KardiaMobile-1L device?

No as above and discussed

4) The electrode on the back of the KardiaMobile 6-L is placed on the leg. Where on the leg can this be placed (knee and ankle only)?

This can be placed on the left knee or left ankle *https://vimeo.com/335613884* video example link as discussed

5) For KardiaMobile-6L is there any evidence looking at whether location/position impacts diagnostic accuracy?

No as above and discussed

6) For KardiaMobile-6L is there any evidence looking at whether location/position impacts proportion of “unreadable” outputs?

No as above and discussed. To support with any ECG it is recommended that the user is seated and as still as possible

7) Significant smoothing of the ECG trace occurs (as indicated by the company YouTube videos). Can you please provide additional technical details regarding the ECG recording? For example filtering applied, any noise reduction algorithms as these may influence subsequent interpretation by a healthcare professional.

Please see patent information attached for US9681814 regarding filtering for Dr David Albert CMO and founder

8) The output of the ECG analysis by the Kardia app (as provided in the IFU) are stated as:
   - Normal
   - Possible AF
   - Bradycardia
   - Tachycardia
   - Unclassified (not Normal, Possible AF, Bradycardia or Tachycardia, and interference not detected)
   - Unreadable (interference)

   However the clinical submission states that “Premature Ventricular Contractions”, “Sinus rhythm with Supraventricular Ectopy” and “Sinus rhythm with wide QRS” are also available options. Can you explain?

As discussed, The IFU is planned to be updated to demonstrate the new determinations as these were only made available 31st March

9) Is any advice given to users when a “possible AF”, “Bradycardia”, “tachycardia” output is given?

YES, as discussed, each determination is mentioned on the app with additional information which can be accessed via the app. Each determination information includes reference that for additional analysis send the ECG for review or share it with your doctor, Kardia does not check for heart attack. Please let me know if you would like any screen shot images of this to support?

10) What are the Kardia app software version names, and when were they released? Has classification/software output changed with software updates?

Kardia App and KardiaMobile released 2015
Version 5.6 released April 2019 - included Tacycardia and Bradycardia
KardiaMobile6L August 2019
Version 5.14 March 31st 2021 - Included new determinations premium mode only and KardiaPro enabled accounts

- Before being called the "KardiaMobile" the device was named as follows (in consecutive order):
  - AliveCor Heart Monitor
  - AliveCor Mobile ECG
- KardiaMobile (single-lead) was originally CE marked in 2015 (under the above name "AliveCor Heart Monitor") and has been in the EU market since then.
- The KardiaMobile device indication for use statement was updated in April 2019 to include two new algorithm results - bradycardia and tachycardia.
- KardiaMobile 6L device, given its similarity to KardiaMobile (single-lead) device in terms of intended use, device characteristics, principle of operation, risk profile, and the scope of the CE mark, was AliveCor self-certified and is available in the EU since August 2019.

11) The device is not intended for use in children, what age cut-off is applied? (Minimum age not stated in IFU).

18 years of age or > the app will not allow account setup with a DOB which is <18 years old

12) KardiaMobile is not intended for use in children and must not be used in adults with cardiac pacemakers, implantable cardioverter-defibrillators or other implanted electronic devices. However are there any other objective criteria for suitability before the device is used (e.g. tremor)?

Good finger dexterity is required as referenced to get a clear ECG the patient needs to remain as still as possible

13) The submission states that “Internet access is not needed when taking a reading”, and that data are transferred via high-frequency sound waves for KardiaMobile-1L and Bluetooth Low energy for KardiaMobile-6L; which enables users to obtain an outcome (e.g. of “possible AF”) without internet. However is it correct that WIFI and/or mobile connection is required if using KardiaCare membership or KardiaPro software?

Internet connection is required only for the ECGs to be uploaded to the GDPR compliant EU cloud. Without wifi the ECGs store on the local smart device and then when wifi is enabled these will then be sent to the cloud (e.g., it is possible to take an ECG on an airplane in flight). KardiaCare and KardiaPro are premium functions as discussed and not within the scope of the required use for this assessment (the basic features are sufficient), but yes wifi is required for ECGs to be uploaded.

14) KardiaBand is no longer available therefore do you agree that all evidence relating to this device should be excluded?

NO the evidence is still applicable single lead ECG technology is exactly the same as KardiaMobile Single Lead

15) GDPR: can you explicitly list what information is transmitted from the device (personal/sensitive)? In what circumstances are these data points transmitted?

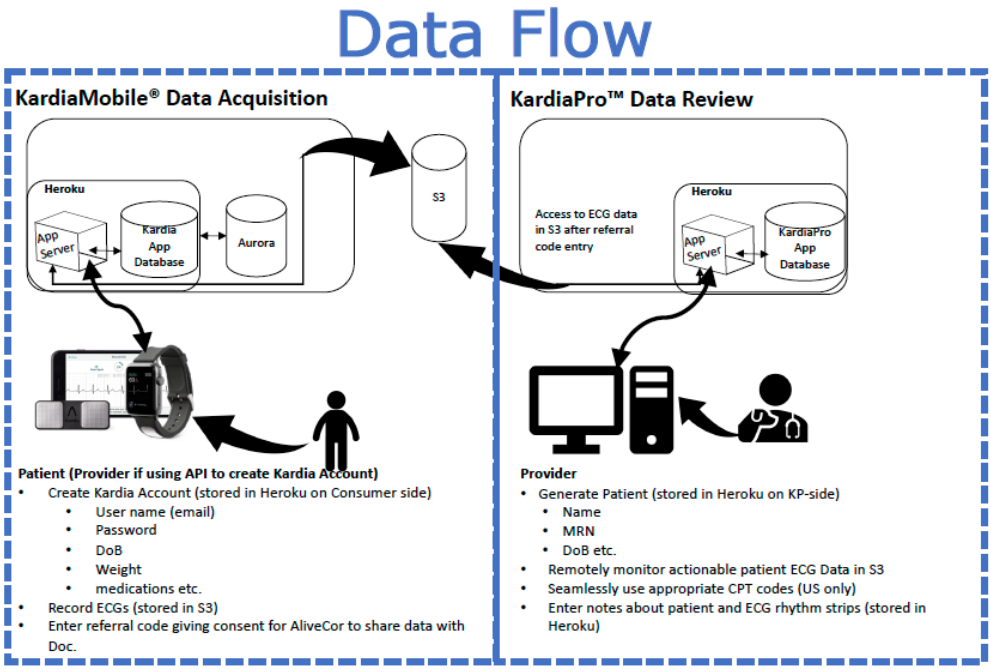
Please see the data flow below. ECG data is updated every time internet connection is resumed.

Information transmitted from the Kardia app to our EU servers includes:

User-provided background information:

- Name
- Email address/password
- Birthday
- Height
- Sex

Optional user-provided medical history information
User-recorded ECG and/or blood pressure data from a connected device



16) Can users opt-out of personal/sensitive data being transmitted?

YES Medical data can opt out, ECG storage can be turned off locally but user name (email), password, DOB and weight always goes to the cloud.

Are users still able to use the device without providing personal/sensitive information?
Minimum requirements for an account is data entry of user name, password, height, weight, sex, DOB and email

17) What does “de-identified personal data” mean in the terms of service?
Outlined in data flow visual

18) Considering the terms of service and privacy policy, what is the formal process when a person withdraws their consent for their data being used?
A user can execute their privacy individual rights as mentioned in the privacy statement and email privacy@alivecor.com to have this removed https://www.alivecor.com/privacy/en/

19) The IFU state that “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.”
However additional annual membership is required for users to have a healthcare professional review their ECG trace (KardiaCare membership).
This is not correct; as discussed this is a misinterpretation as a HCP is not involved with KardiaCare. If a patient falls under the care of a HCP who advises the use of KardiaMobile the patient can send or share the ECGs to their HCP as requested. KardiaCare does not support this function in a medical situation and is a premium function supported by a cardiac physiologist not a HCP, again this is not within the scope of this assessment and not applicable.
What specific information accompanies the trace when reviewed by a professional?
Name, Heart rate, DOB, Time and date stamp, algorithm determination, filter information, ECG trace

Economic model

20) Could you give us any “heads up” information regarding the economic model, in terms of:
- Software used (Excel, other).

Yes Excel model

- Model structure (decision tree, Markov)

It will be decision tree plus Markov model

Appendix 4

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Expert Engagement Meeting

GID-MT554 KardiaMobile

Date: **14 March 2021**

Time: **12:30 to 14:00**

Documents

MIB: **https://www.nice.org.uk/advice/mib232**

MTG Scope: **https://www.nice.org.uk/guidance/indevelopment/gid-mt554/documents**

NOTES

In Attendance:

NICE: Kim Carter (KC), Ying-Ying Wang (YYW), Cheryl Pace (CP), Chris Chesters (CC)

Newcastle EAC: Kim Keltie (KK), Emma Belilios (EB), Kathryn Fletcher (KF)

Experts:

Kevin McGibbon (KM), Arrhythmia Clinical Nurse Specialist, University Hospitals of North Midlands NHS, involved in screening using KardiaMobile and projects managing patients using KardiaMobile

Adrian Brodison (AB), Consultant Cardiologist, University Hospitals of Morecambe Bay NHS Foundation Trust, uses KardiaMobile in clinical practice

Lis Neubeck (LN), Professor of Cardiovascular Health, Edinburgh Napier University, involved various studies using KardiaMobile (incl. first study on humans)

Matthew Reed (MR), Consultant, NRS Clinician and RCEM Professor of Emergency Medicine, NHS Lothian, CI on IPED study.

Ruth Chambers (RC), Ex- Staffordshire clinical lead for technology enabled care services programme, digital workstream and Honorary Professor Keele University, Visiting Professor Staffordshire University, working promoting KardiaMobile (distributed around 400 across Staffordshire), recent publication in BJGP using KardiaMobile across 16 practices https://bjgpopen.org/content/5/2/BJGPO.2020.0169.

Apologies: Victoria Fitton, Shouvik Haldar, Shona Holding

Welcome and introductions

KC requested that participants inform her of any Conflicts of Interest that they have not declared previously.

Questions for the professional experts by theme: (see below)

Classification of arrhythmia and diagnosis of atrial fibrillation

The technology and population

The clinical pathways

Understanding the evidence

Next steps

Notes will be circulated week commencing 19 April 2021 for review, final notes will be included in the correspondence log and shared with the Committee.

Questions for discussion

Classification of arrhythmia and diagnosis of atrial fibrillation

1. The outputs from the Kardia app are the following:
   - Normal, possible AF, bradycardia, tachycardia, unclassified and unreadable

   In clinical practice:
   a) What arrhythmias could “Unclassified” include?
   b) What would Atrial Flutter be categorised as?

Response:

a) The experts agreed that there is some overlap between 'unclassified' and 'unreadable'. Default for anything not classified as one of the identifiable rhythms (e.g. left bundle). The newer algorithm has an increased range of classifications resulting in fewer traces being categorised as 'unclassified'.

b) The experts thought categorisation of atrial flutter would depend if the flutter was regular or irregular. One thought an irregular flutter might be classified as AF, regular flutter might be classified as tachycardia (it would then be correctly categorised when the trace was reviewed/over-read).

2. Would clinicians accept a single-lead trace from a KardiaMobile device in order to confirm/diagnose AF? In practice how could a patient get an NHS clinician to review their KardiaMobile trace?

Response:
This would depend on local policy. European Society of Cardiology (ESC) guidelines are very clear that a single lead trace is acceptable for diagnosis of AF, however, UK guidance is less clear. In practice, local policy varies.

The experts agreed that the benefit of KardiaMobile was that it recorded symptom driven AF, and that clinical review of KardiaMobile traces is necessary (as long as the ECG trace is clear), however implementation of this varies across the NHS depending on local policies. In secondary care, some Centres would rule out AF following clinical review of a normal single lead trace. If KardiaMobile trace showed AF, diagnosis would be confirmed with a 12 lead ECG. If the 12 lead ECG showed normal sinus rhythm, one expert advised that they would still be likely to assume the KardiaMobile trace was correct, and that the patient was in AF when the single lead trace was taken. Patients with sporadic palpitations can record a trace whenever they get symptoms, whereas it would not be possible to get them on to a 12 lead ECG in time. One expert said that only abnormal traces would be over-read.

In primary care, if a patient had AF detected on a single-lead KardiaMobile trace, GPs would confirm AF diagnosis if the trace was clear, but would also follow up with a 12 lead ECG (rule in). Some would however trust KardiaMobile 6 lead trace for rule-out. [EAC note: Both KardiaMobile-1L and KardiaMobile-6L are both in scope for this assessment]. RC provided a link to a paper she co-authored on KardiaMobile implementation in East Staffordshire (Mathew & Chambers, BJGP Open 2021).

KardiaMobile is particularly useful as a quick screening device. One expert reported that a survey on KardiaMobile revealed a wide variety of uses, including pharmacists reviewing patients' traces and GP practice nurses using it routinely to check people with comorbidities that make stroke more likely. YYW clarified that the scope of this guidance is longer term monitoring of people with confirmed or suspected AF. Therefore screening and single time point testing are out of scope of this assessment.

If the device is issued by an NHS organisation, there will be a clear route for clinical review of the trace. If the patient has purchased the device themselves, there is no automatic route, the patient would need to contact their GP or present to the Emergency Department (ED) if

they had concerns. One expert reported they are seeing people in the ED who have taken traces on their phones or wearable devices.

One expert estimated the total cost of a stroke (NHS and Social Care) is approximately £30,000. There are published studies showing that KardiaMobile is cost effective in terms of stroke prevention (and probably cost saving), but they are all in screening populations. The experts were not aware of any cost effectiveness studies in monitoring populations, but as this population will be at higher risk of stroke they would assume KardiaMobile is more cost effective in this population. The additional benefit of the device is that it is reusable, however one expert confirmed that they set up the app with the user in clinic, and advise using non-identifiable information to do so.

The technology and population

3. What is the population who are the most likely to benefit from KardiaMobile?

Response:

The device has been used by healthcare professionals; for instance, pharmacists used in people who presented with palpitation and nurses used in people with co-morbidities.

Older adults (aged 65 years or over), and anyone with comorbidities that put them at increased risk of stroke would benefit from the device. The experts agreed that patients <65 would be unlikely to have AF. One expert thought that there was therefore no clear benefit from the single lead KardiaMobile device to the younger population (although the 6 lead KardiaMobile device may pick up conditions that are more common in <65s) and that there needed to be some caution around self-screening in this age group. Another expert thought that KardiaMobile could be very useful in reassuring younger patients with palpitations that their symptoms were not due to AF. One expert has used the KardiaMobile 6 lead device in elite athletes to look at other elements of cardiac risk, but this population would be out of scope for this assessment as the focus is not on AF.

For screening populations, would usually want continuous monitoring. KardiaMobile is good for quick trace when patient gets symptoms, but doesn't give yield.

KardiaMobile is not suitable for use patients with syncope (as device is patient activated).

One expert has used KardiaMobile for AF patients post-ablation to check for recurrence of AF in place of Holter monitors. Patients were required to take a trace 4 times a day. The technology was well received by patients. Another expert is about to start a similar mini-trial of KardiaMobile on patients post-surgery. In primary care, the device may be used to monitor heart rhythm in people with comorbidities. From a patient perspective, KardiaMobile is preferable to wearing a Holter monitor for 24 hours or longer. It is also a cheaper option.

Patients do need to learn 'tricks of the trade' to self-monitor effectively and to record a clear ECG trace, and may require additional training on how to use the device and the app. Applying too much pressure was a common issue with users, as was interference from

surroundings. Patch monitoring technology may be preferable for some patients- gives continuous monitoring (not patient activated), more comfortable, avoids usability issues, and is less invasive than a Holter monitor – but is more expensive and not reusable. One expert reported that Bardy patch monitors are now available through procurement in Scotland. In the NHS, funding may not be available for patch devices. The experts thought there was a place for KardiaMobile as well as 24 hour to 14 day Holter monitor and patch monitor options in the patient pathway for the identification of paroxysmal AF. Patch monitors are a more expensive option but may be better for some patients.

Two of the experts are involved in a trial of KardiaMobile that includes the option to pay for the premium service. For £100 a year, patients in the community can access expert opinion when needed. They have just issued the last device and will start sending out patient surveys. Anecdotally, patients' response has been positive. They expect to have results within next couple of months, which they would be willing to share AiC with the Committee. Experts agreed that no additional resources is needed for interpretating ECG traces recorded by the device. In primary care, GPs are trained to read and interpret ECG trace.

KK clarified that a premium service (KardiaCare) does not provide access to an NHS cardiologist. The Company have clarified that the trace is reviewed by a professional employed by a private firm. AliveCor is based in the US, so there may be data sharing issues.

The EAC has identified 5 distinct patient sub-groups from the available evidence:

- Patients with palpitations who have tried 12 lead ECG but symptoms are too far apart to capture
- Patients with AF post treatment to check for recurrence
- Patients with AF to record burden
- Patients post-surgery with secondary (transient) AF
- Patients who have had a stroke or TIA (to rule out AF as a cause)

The experts agreed that these were relevant groups where KardiaMobile may be used, and that the underlying risk of AF is different across these groups.

4. Is this a substantial limitation of the device in relation to age, and patients with cardiac implantable devices?

Response:

These were not considered limitations of the device. AF is rare in people aged under 18. The age restriction (KardiaMobile is only recommended for patients over 18) was agreed not to be a substantial limitation as patients <18 would not normally need the device. One expert commented that they saw no technical reason why the device would not work on someone under 18. For legal reasons, the Company require that only patients aged 18 or over can set up accounts. Patients with cardiac implantable devices would also be unlikely to need this type of monitoring.

5. What proportion of patients would struggle to use KardiaMobile?

Response:

The experts thought that most people would be able to use KardiaMobile with proper training, although patients over 75 are likely to need more support and access to an internet-enabled device (age and socioeconomic factors may contribute). People who lack experience using mobile devices may find it difficult to use the device.

Patients with Parkinson's disease find the 6 lead KardiaMobile device difficult to use. The current single-lead version can be rested on a bench making it more usable for people with tremor. The original devices were clipped to the back of the phone which created more usability issues.

In the community, there may be connectivity issues.

6. Can you estimate the proportion of patients in whom KardiaMobile would not be appropriate due to lack of suitable mobile devices?

Response:
The experts thought that between 10-20% of the population don't own devices that would be compatible with KardiaMobile. One expert was involved in a study on a different cardiac app (Fibricheck), which suggested that most people had access to a suitable device through friends and family even if they didn't own one themselves. However that approach would be less suitable for longitudinal monitoring using KardiaMobile.

Some android phones are not compatible with KardiaMobile. Company can provide a list of compatible phones. Some phones not on the list do work with KardiaMobile, although phone software updates and Kardia app updates have affected accessibility. One expert noted that their Centre is considering buying phones to loan to patients to improve accessibility (cheapest compatible phone costs around £100). Accessibility may be a bigger concern in areas with high levels of deprivation.

One expert referred to an Ofcom survey which suggested that 80% of all UK adults have smart phones but only 50% of over 70s. One expert noted that people who don't routinely carry their mobile device with them may struggle to use KardiaMobile effectively for monitoring symptoms.

The clinical pathways

7. Can the diagnosis of AF be from a standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 seconds?

Response:

Current European Society of Cardiology (ESC) guidelines state that a single lead trace is acceptable for diagnosis of AF (see also Q2). There is no definitive UK guidance on this.

KK asked if there would be any benefit from the 6 lead KardiaMobile device over the single lead device for diagnosis of AF. One expert thought there would be no benefit in diagnosis of AF. One expert thought that the 6 lead trace would be helpful in identifying/excluding other possible causes for symptoms. One expert thought the 6 lead trace would give more angles to pick out a clear trace. One expert noted that they thought it would take a long time for GPs to accept a single lead trace as an alternative to 12 lead ECG for diagnosis.

As the patient moves down the pathway the experts agreed that it becomes more likely that they will be referred for a 12 lead ECG at some point, as this will pick up additional useful information. Patients with suspected paroxysmal/sporadic AF will most likely end up on continuous monitoring.

Understanding the evidence

8. Some studies have reported “AF/flutter” or “atrial arrhythmia”. Are both of these suitable for inclusion in terms of clinical evidence to support this guidance which focuses on Atrial Fibrillation only?

Response:
The experts advised that atrial flutter and AF, are separate rhythms. However if reported together in the literature then they should be considered within this assessment report (as it would include AF).

9. One diagnostic accuracy study compared KardiaMobile again traditional transtelephonic monitoring (TTM) using (Pacetrack, Mednet Healthcare Technologies or CarryAll EZ Monitor, Instromedix). Is TTM used in NHS, and is this considered a valid comparator?

Response:
The experts agreed that TTM does not reflect current NHS practice.
Two of the experts had not heard of TTM.
One expert thought that usual practice would be Holter monitor, therefore they did not consider TTM a valid comparator.
One expert was familiar with TTM (their Centre has used it for transmission of results from some pacemakers) and noted that there are other issues with this method.

10. Some studies include a population presenting at A&E with palpitations, the intervention arm are given the KardiaMobile device and the comparator arm appears to have “watchful waiting” approach. What proportion of patients presenting with palpitations undergo “watchful waiting”?

Response:
MR clarified that the comparator arm of the The Investigation of Palpitations in the ED (IPED) study MR - IPED study was not a ‘watchful waiting’ arm, it was a standard care arm

(according to local policy), which may be watchful waiting in some areas. The study tried to pick up different types of standard care, as standard care varies across Centres.

One expert noted that risk of stroke in AF is highest in the first four months after diagnosis so would not want to wait.

If standard care cannot be defined, this makes the assessment more problematic. One expert noted that there is a distinction between 'ideal' care and 'standard' care. Holter monitor is the reference standard at many Centres, but Holter monitors are not well tolerated by patients so compliance is poor.

One expert thought that KardiaMobile was a useful additional option, which fitted in the patient pathway somewhere between a Holter monitor and an implantable loop recorder. Bardy patch monitors were another option, but they are expensive and there is a wastage component which KardiaMobile does not have. KardiaMobile is a reusable, simple and relatively inexpensive solution.

The experts agreed that the COVID-19 pandemic had necessitated a move to remote consultation where possible. KardiaMobile allows patients to take recordings at their convenience and not come to high-risk areas (GPs, hospitals) to have their ECG reviewed as clinicians can view remotely.

KK asked if the requirement for traces to be interpreted by a clinician was feasible across the NHS. The experts agreed that this was standard practice already.

Appendix 5

MTG Medtech Guidance:

Expert contact details and declarations of interest:

Expert #1	Adrian Brodison, Clinical lead cardiology, University hospitals of morecambe bay NHSFT, [redacted]
	Nominated by:
	DOI: NONE
Expert #2	David Ferguson, Arrhythmia Advanced Nurse Practitioner, University Hospitals of Morecambe Bay NHS Foundation Trust, [redacted]
	Nominated by: Expert above
	DOI: NONE
Expert #3	Kevin McGibbon, Arrhythmia CNS, NHS, [redacted]
	Nominated by company :
	DOI: YES AliveCor/KardiaM.obile have approached me and I have agreed to film a testimonial by healthcare professional that they may be using in their TV/social media adverts for the device. There is no payment involved.
Expert #4	Lis Neubeck, Professor, Edinburgh Napier University, [redacted]
	Nominated by: Company
	DOI: NONE
Expert #5	Matt Reed, Consultant, NRS Clinician and RCEM Professor of Emergency Medicine, NHS Lothian, [redacted]
	Nominated by: Company
	DOI- YES Direct - financial The Emergency Medicine Research Group Edinburgh has received sponsorship for the EMERGE10 conference in 2018 from various companies including Medtronic Inc, AliveCor and iRhythm Technologies. 2018 2018 Non-financial professional

	MR has been supplied with Zio XT monitors and ECG analysis services free of charge for research purposes from iRhythm Technologies between 2015 and 2017. MR has received funds for consultation from Medtronic Inc in 2018 and 2019. 2015 2019 Non-financial professional MR is supported by an NHS Research Scotland Career Researcher Clinician award. 2012 To date
Expert #6	Dr Ruth Chambers, Clinical lead for technology enabled care programme, Staffordshire Sustainability & Transformation Partnership c/o employment by Stoke-on-Trent CCG, [redacted]
	Nominated by: Company
	DOI: NONE
Expert #7	Shona Holding, Cardiovascular advanced nurse practitioner, Affinity care, [redacted]
	Nominated by:company
	DOI: NONE
Expert #8	Dr Shouvik Haldar, Consultant Cardiologist & Electrophysiologist, Royal Brompton & Harefield Hospitals, [redacted]
	Nominated by: company
	DOI: NONE

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it?	Expert #1: Have used Kardia mobile for several years now. We search for symptomatic arrhythmias including AF, SVT, VT etc Yes as above	

	Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Yes frequently I hear lots of people using them We specifically preclude other specialities from using them other than cardiology although are about to do a trial will post stroke patients to look for AF no	
		Expert #2 I have been using KardiaMobile since the autumn of 2017. We have 60 devices in our trust which we loan out to patients for 2 months at a time, or shorter if we obtain symptom correlation. We use it in our arrhythmia service to identify arrhythmias in patients with symptomatic palpitations. We have developed a standard operating procedure for its use and provide patients with detailed instructions on how to use it, based on the company's own literature.	

		We encourage patients to email us ECG rhythm strips recorded on their KardiaMobile device when they are symptomatic with palpitations. The email is checked every two days and I run an Alivecor clinic on Friday where I telephone patients to discuss results of their ECG rhythm strips. Currently using I know of several other NHS centres who use it. Some in a similar way to us and some who use it for identification of silent AF both in primary and secondary care. The innovation agency in north west England had a “detect, protect, perfect” program a couple of years ago where they were lending devices to GP’s, the uptake however was slow. Yes stroke specialists use it. I occasionally use KardiaMobile rhythm strips to refer patients for EP studies and ablation procedures if it's all we have	
		Expert #3 I have been using these devices for some time and continue to do so. They are widely used in the NHS, particularly in Primary care and have	

		been issued to Primary care in large numbers by the Academic Health Science Networks (AHSN	
	–	Expert #4 I am very familiar with the technology, having undertaken the first validation study in humans, and the first screening study in community pharmacies. The protocol for this study was then used in numerous studies globally, including in Scotland, where it has been demonstrated that detection of AF rates were significantly elevated, and that patients who were detected had high risk of future stroke. Please note my expertise relates to atrial fibrillation detection, and not to the use of the new Kardia 6L. However, I see this technology as an advantage as it adds to the range of conditions that could potentially be detected. One of the previous challenges with scaleability was the number of 'unknown' diagnoses (roughly 10%) but improved algorithms for detection of sinus tachycardia/ sinus bradycardia, etc should reduce this burden. - In Scotland, uptake has been patchy and dependent on local champions. Recommendation	

		of it's use for clinical purposes should increase uptake, particularly if it is added to national procurement lists - A range of clinicians have successfully used this technology including nurses, cardiologists, pharmacists, podiatrists and general practitioners. In a recent qualitative study we have done, as part of a Horizon 2020 funded study 'digital risk reduction in atrial fibrillation in Europe', participants highlighted other opportunities for detection such as dentistry. Because of the ease of use, it could be used for self-screening. This is currently being investigated in research studies. - A key challenge is ensuring that once AF is identified it is appropriately managed. We have worked on projects embedding this technology in general practice coupled with electronic decision support tools.	
	–	Expert #5 I have extensive experience of Kardia/AliveCor both through clinical research (IPED study; see below) and introducing the Kardia technology into clinical care through the establishment of our Smartphone palpitation and pre-syncope ambulatory care Clinic (SPACC) service.	

		All patients aged 16 years or older presenting to the Emergency Department (ED) or Acute Medicine Unit (AMU) of the Royal Infirmary of Edinburgh (RIE) with palpitations or pre-syncope, whose ECG is normal, who have a compatible Apple/android phone, tablet, or watch, and in whom an underlying cardiac dysrhythmia is possible, are offered an appointment at the SPACC, which was based in an ambulatory care clinic setting beside the ED. Further details of the service available at https://www.mdpi.com/1010-660X/57/2/147 Emergency Department/ AMU RIE, Smartphone Palpitation Service SOP: Available online: https://www.emergeresearch.org/wp-content/uploads/2015/12/Palpitation-Ambulatory-care-pathway-v3-13-07-2020-FULL-VERSION.pdf (accessed 6 February 2021). The technology is used widely on an ad hoc basis (and in some centres as part of a more organised care pathway) in cardiology clinics but less so in other settings. Being available to the public via Amazon, it is something increasingly that patients are purchasing and attending with symptomatic rhythms to the ED (similarly with the Series 4 Apple watch).	

	–	Expert #6 I have been responsible for writing a 'How to use AliveCor KardiaMobile device' guide for clinicians with a medical student Dr John Marszal – in 2017 -0 for general practice clinicians. I have organised & chaired 4 educational workshops for GPs & nurses across Staffs to learn about best practice in clinical management of AF & use of AliveCor KardiaMobile for AF screening in frontline primary care; 2018-2020. As a result, we have deployed 400 AliveCor KM lead 1s across 113 Staffs practices (I wrote bids for funds successfully from NHSE Estates & Technology Transformation Fund on behalf of Staffs CCGs.) + 10 AliveCor lead 6s. Recently published article with junior doctor describing usage in one of the 6 Staffs CCGs. We advise that practice nurses screen patients whom they are reviewing for long-term conditions cae eg annual review who are not known to have AF - for AF with AliveCor devices; or opportunistically at practice 'flu clinics. We have also produced webinars for practice teams to emphasise potential of digital aids for cardiovascular conditions – for screening & clinical managements – this included	

		demonstrations of use of AliveCor KM for clinicians by clinicians; and patients' own perspectives. The webinars were watched by circa 300 clinicians & were well evaluated (September 2020-January 2021) I do not know if secondary care & community care clinicians use AliveCor in these ways. I stopped practising as a GP in 2017- so I do not screen for AF on frontline myself. Some of the CCGs' workshops were supported by	
	–	Expert #7 I have extensive experience of using kardia. Have used it in my daily practice for 5 years. Yes Yes but less, often as currently using a different device	

		I have been involved in auditing data of a palpitations pathway using kardia. Not sure but aware some centres are setting up palpitations pathway using kardia. Some GPs may use them for screening ..use if pick up an irregular pulse I work within a community cardiology service. I have been involved in auditing data of a palpitations pathway using kardia.	
	–	Expert #8 I am very familiar with the technology. I have the device which I use to show patients in clinic. I recommend the device to patients to buy if we are embarking on a journey to capture arrythmias I am not involved in research using it. It is being increasingly recommended especially by EP cardiologists but there is significant geographical variation in popularity.	

		It is being increasingly used but overall penetrance is small. The speed of uptake is going to be fast particularly if patients purchase themselves. Yes – sometimes neurology when dealing with cryptogenic stroke. N/A as I am cardiologist.	
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have done bibliographic research on this procedure. no I have done research on this procedure in laboratory settings (e.g. device-related research). no I have done clinical research on this procedure involving patients or healthy volunteers. We have published an poster in HRC I have published this research.	

		As above	
		Expert #2 I have done bibliographic research on this procedure. Yes I have done research on this procedure in laboratory settings (eg. device-related research). No I have done clinical research on this procedure involving patients or healthy volunteers. Yes I have published this research. Yes I have had no involvement in research on this procedure. n/a I published a poster presentation for the Heart Rhythm Congress on how we use the device and results to date.	
		Expert #3 I have done bibliographic research on this procedure.	

		I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure. Other (please comment)). I have not been involved in research or development of this device.	
	–	Expert #4 I have done bibliographic research on this procedure I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research.	
	–	Expert #5 I have done clinical research involving patients.	

		I was the Chief Investigator (CI) of the Investigation of Palpitations in the ED (IPED) study: Reed MJ, Grubb NR, Lang CC, O'Brien R, Simpson K, Padarenga M, Grant A, Tuck S, Keating L, Coffey F, Jones L, Harris T, Lloyd G, Gagg J, Smith JE, Coats T. Multi-centre randomised controlled trial of a smartphone-based event recorder alongside standard care versus standard care for patients presenting to the Emergency Department with palpitations and pre-syncope: the IPED (Investigation of Palpitations in the ED) study. Lancet eClinical Medicine 2019; 8: 37–46; PMID: 31193636 DOI: 10.1016/j.eclinm.2019.02.005 This showed that the Kardia smartphone-based event recorder increased the number of patients in whom an electrocardiogram (ECG) was captured during symptoms over five-fold to more than 55% at 90 days compared to standard care and concluded that this safe, non-invasive and easy-to-use device should be considered part of on-going care to all patients presenting acutely to ED or acute medicine with unexplained palpitations or pre-syncope. I am also CI on the implementation study published in Medicina:	

		Reed MJ, Muir A, Cullen J, Murphy R, Pollard V, Zangana G, Krupej S, Askham S, Holdsworth P, Davies L. Establising a smartphone ambulatory ECG service for patient presenting to the Emergency Department with pre-syncope and palpitations. Medicina https://www.mdpi.com/1010-660X/57/2/147	
	–	Expert #6 I have not done bibliographic research on this procedure; instead I have done service redesign – as described above; overseeing clinicians' education/confidence/competence to use this procedure on their patients in their own workplace settings. I have published this as service redesign – not research – as above Mathew S and Chambers R. Improving the utility and sustainability of novel health technology to improve clinical outcomes for patients: an East Staffordshire experience of screening for atrial fibrillation with the AliveCor KardiaMobile. BJGP Open February 2021. DOI: 10.3399/BJGPO.2020.0169 https://doi.org/10.3399/BJGPO.2020.0169	

	–	Expert #7 I have had no involvement in research on this procedure.	
	–	Expert #8 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure. Other (please comment)	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: As we have bene using it for some time it is now an integral part of our practice and is much better than our old cardiocall event recorders and much cheaper Established practice and no longer new. In my view yes	
		Expert #2 It was innovative in 2017, it has become well established now and because the device can be used within the patients home it is excellent for identifying ECG changes in patients with symptomatic palpitations. It can also be used for the opportunistic detection of AF and is more reliable than pulse checks in general practice. The major advantage of the device is that it is free to download the application software and the device itself is inexpensive. Established practice and no longer new. no	

		A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. no Definitely novel and of uncertain safety and efficacy. no The first in a new class of procedure. yes	
		Expert #3 I would say that this particular device is innovative. The gold standard for AF diagnosis is a 12 lead ECG. Feeling the pulse manually or some other wearable technology give an indication of if a pulse is irregular. This falls in between and gives a strong indication if the user has Atrial Fibrillation (AF). Established practice and no longer new. Yes, A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	

		Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	
		Expert #4 This technology has been widely tested over the last 10 years and the data suggest high level of diagnostic accuracy. Use of single-lead ECGs in the European Society Guidelines is a class 1 recommendation, and much of the evidence for this has been developed using KardiaMobile technology A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	
		Expert #5 In my opinion use of the AliveCor/Kardi is becoming increasingly used in clinical practice in Cardiology services. Use in an ED and acute medicine service is definitely novel.	

		I would say it is 'Definitely novel but has increasing evidence of safety and efficacy'	
		Expert #6 Established practice and no longer new.	
		Expert #7 Use of kardia is innovative and a novel concept , associated with an increased diagnostic yield as used during symptoms and immediately following detection of an irregular pulse Established practice and no longer new.	
		Expert #8 It is a novel concept as it gives the patient the power to control their data. Established practice and no longer new.	

		A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: Both replace and additional	
		Expert #2 We have been using it to replace ambulatory monitoring in arrhythmia detection, in this respect it can definitely replace standard care in some cases although the trace quality with ambulatory monitoring is of a better quality. Ambulatory monitoring is restricted by time and cost, this is a value for money alternative.	
		Expert #3 This replaces feeling pulses in some scenarios and is an additional technology in others.	
		Expert #4 This would depend on recommendations from NICE. ESC recommends that diagnosis of AF can	

		be made on a single-lead ECG without need for confirmatory 12-lead ECG. If we accept this is a valid technology, then it could reduce the need for 12-lead ECGs which require more time to take, need a dedicated space, and need specialist interpretation.	
		Expert #5 Definitely has the potential to replace the 24hr Holter from its position as current standard care.	
		Expert #6 It is part of usual service in majority of practice teams that have at least one AliveCor KM device- across Staffordshire general practices	
		Expert #7 It will replace need for 24hour or prolonged holter monitoring in most cases. But may be used in addition to prolonged monitoring	
		Expert #8 It is very innovative and novel but overall likely to be in addition to standard care. In some instances, has the potential to change standard of care for investigating arrhythmias	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Our previous event recorder was a cardiocall which is an old device and quire cumbersome	
		Expert #2 Currently ambulatory monitoring is widely used for arrhythmia detection in symptomatic patients, problems occur when patients do not have symptoms over the period of time the monitor is in place.	
		Expert #3 Opportunistic manual palpation of pulses to look for undetected AF.	
		Expert #4 For diagnosis of AF, 12-lead ECG is currently required, although single lead ECG is considered acceptable in ESC guidelines	
		Expert #5 Repeated unrewarding 24hr Holter monitors. Although increasingly AliveCor/Kardia is being used in clinical practice in Cardiology services (although without much research evidence for its safety and efficacy). Use in an ED and acute medicine service is more novel.	
		Expert #6 Ad hoc feeling of a patient's pulse to detect AF by a clinician.	

		If concerned might be AF maybe arrange a 12 lead ECG or holter to be worn from 2-14 days; but not every general practice has an ECG machine or expert clinician to interpret the tracings. Most practices would need to refer patient for wearing a holter (costly procedure); whereas AliveCor KM device can be used there & then; or purchased by patient who can save tracings to show clinician.	
		Expert #7 Prolonged monitoring but in some arrhythmia centres, lead 1 device is used to monitor intermittent symptoms	
		Expert #8 When investigating arrythmias – 24-72 holter or 7 day holter in first instance.	
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: We also used Diagnsticks which is similar but only for patient who do not have or can not use a mobile phone as they are much more expensive.	
		Expert #2 Yes We also “Mydiagnostick” devices in place of KardiaMobile for patients without a smartphone/tablet or who are not confident using the Kardia/Mobile device due to technological or	

		dexterity issues. KardiaMobile is also not recommended for paediatric patients and so we use Mydiagnostick to identify arrhythmias in paediatric patients.	
		Expert #3 There are many similar technologies on and entering the marketplace for AF detection, far too many to list. They have varying modes of operation and varying methods of detecting AF with variable accuracy and reliability. This device has high degree of specificity and sensitivity and connects to a smart phone or tablet to give a nice visual of the ECG that can be easily transmitted by e-mail. It also gives an excellent estimation of heart rate based on a multiplication of a 30 second ECG. Other devices will have some of these functions.	
		Expert #4 There are a range of single lead ECGs on the market, some which are personally activated, eg Withings watch, Apple watch, Fitbits. There are also Zenicor, MyDiagnostick, and other single lead patch technologies, eg Bardy Patch, QardioCor, and ECG 24. KardiaMobile is different in having 6-lead ECG capability, and validated algorithms for detection of more than just AF.	
		Expert #5	

		Continuous ambulatory ECG monitors are available (e.g. BG mini from Preventive and Zio from iRhythm) but are more expensive and are only able to record continuously for 14 days meaning that if the patient's palpitations are less frequent they may not be detected. Investigation of palpitations does not require a continuously recording device as unlike syncope (blackout), patients are conscious when they have their episode and are therefore able to use an event recorder such as the Kardia/AliveCor. Other more traditional event recording devices are also on the market but not linked to smartphones. Other smartphone based pulse rate devices are also available such as through Samsung, and other healthcare companies (e.g. Preventicus Heartbearts) but do not record an ECG tracing, only a pulse rate through the phone camera.	
		Expert #6 I'm aware that the Apple watch has facility to record heart tracing via pulse rate; and some sphygmomanometers do. But I don't know how reliable they are. Same for fibricheck device- am not familiar with it & don't know how reliable it is.	
		Expert #7 Smart watch: produces very clear ECG trace but is not NICE approved. Zenicor produces lead I trace. No mob phone is needed, easy to use, device is size of a mob	

		phone so is also portable. unable to see ECG during recording. The ECG is sent to a database. Patient details have to be entered to database before use. Produces clear tracings most of the time. Has callipers so can measure intervals more accurately	
		Expert #8 No – not that perform as well as this device which also has a favourable cost profile.	
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Easy to use, cheap, widely available, can send results over the internet, we can buy lots of them so can expand the service.	
		Expert #2 Patients are able to record a single lead ECG trace when they are symptomatic with palpitations, this can then rule in or rule out an arrhythmogenic cause for their symptoms if they are able to record a trace at the exact time of experiencing symptoms. Arrhythmias can now be diagnosed that previously were not captured on any kind of ECG monitoring. Patients can also use the device to detect asymptomatic AF if it is suspected.	

		Expert #3 AF causes blood clots and strokes. This technology aids AF detection. When AF is detected medication can be given to prevent strokes. AF is more common with advancing age and as the average age of the population increased, AF is becoming more common world-wide.	
		Expert #4 Rapid detection and early implementation of management plans that could potentially prevent stroke. In our work with patients in the use of this technology, patients who have not got a diagnosis are generally interested in the tech, but not worried about it, and those who have been diagnosed are relieved and grateful to have AF detected	
		Expert #5 Easy to use and distribute from hospital and community health settings. Relatively inexpensive. Reusable Increased efficacy in detecting symptom rhythm correlation. Also a ‘negative’ finding of sinus rhythm/sinus tachycardia or ectopic beats during symptoms is as valuable as detection of a cardiac dysrhythmia as this will allow reassurance that the patient does not have a	

		cardiac dysrhythmia as the cause of their palpitations.	
		Expert #6 Easy to use, quick (30 seconds), likely to detect AF if patient has irregular heart rate during the test.	
		Expert #7 Using this technology means heart rhythm can be captured during symptoms… often 24 hour holters miss symptomatic episodes	
		Expert #8 Quicker time to (accurate) diagnosis for investigating arrythmias / following up for recurrence post AF management (DCCV or catheter ablation). User friendly Patient orientated and patient in control of recording symptoms and capturing data which should give excellent symptom – rhythm correlation.	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Symptomatic patients Asymptomatic patients who need to change therapies based on +ve findings ie AF post stroke or TIA	
		Expert #2 Yes, patients with symptomatic palpitations and stroke patients in who we may suspect AF but it has not been proven.	
		Expert #3 As it needs to be linked to a smartphone or tablet, there is the potential for digital exclusion. AF is far more common in advancing age and so is digital exclusion so the younger AF patients would benefit more in personal use. When used for AF detection by health care professionals this evens out.	
		Expert #4 Our multicountry patient-level meta-analysis of 141,220 screened individuals suggest that the cost benefit is adults over 65 years. The benefit grows with increasing age and stroke risk	
		Expert #5 1) Patients with palpitations to detect atrial fibrillation, atrial flutter and SVT.	

		2) Stroke; CVA/TIA patients to detect asymptomatic paroxysmal atrial fibrillation Asymptomatic patients to detect asymptomatic paroxysmal atrial fibrillation allowing treatment with anticoagulation where appropriate and reducing stroke/TIA primary occurrence.	
		Expert #6 Those with comorbidities, aged>60 for whom atrial fibrillation is more likely than younger/healthier people.	
		Expert #7 Those with intermittent palpitations lasting longer than 30 seconds. Those who have irregular pulse detected.	
		Expert #8 Most would benefit. Only those who were particularly elderly of had medical problems such as severe rheumatoid arthritis may find it challenging to use.	
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system?	Expert #1: Yes undoubtedly it already has in our organisation	
		Expert #2 Yes, it can reduce the number of ambulatory monitors used both in primary and secondary care. This could lead to less hospital	

	Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	visits and a shorter wait for diagnosis. Patients are also able to buy their own device. We have a dedicated email address so that patients can send in ECG traces for diagnosis. If they have tried KardiaMobile with us and not had any symptomatic episodes they are able to buy their own device and continue to send in any symptomatic traces.	
		Expert #3 I am just starting a pilot to issue my patients with these devices for a 6 month trial. A satisfaction survey will help us understand if the patients felt it helped with fewer hospital/GP visits in managing their condition. When used in screening programmes (as I and others have done previously) it has led to AF detection and stroke prevention medication issue.	
		Expert #4 Yes, this could reduce the number of visits to hospitals, especially in areas with limited access to ECGs. In rural and remote settings, the technology could be posted to patients. Because the data is cloud based it could be viewed at a hub, and recommendations for treatment could be implemented without the need for patients to travel. It is considered highly likely that early detection of AF will prevent stroke, although prospective studies are ongoing. Screen-detected AF	

		patients generally have high risk for stroke and warrant anticoagulation.	
		Expert #5 Definitely. Will allow earlier pick (or ruling out) of atrial fibrillation, atrial flutter and SVT in patients with palpitations. Reduced fruitless investigation. Better detection of asymptomatic paroxysmal atrial fibrillation in stroke/TIA patients allowing treatment with anticoagulation where appropriate and reducing stroke/TIA recurrence.	
		Expert #6 Main benefit is increased diagnostic rate for AF, then clinician starts anticoagulation treatment if justified by score; and a stroke is potentially avoided- saving hospital admission/death/loss of job & increased social care costs. Thus improved clinical & social outcomes/saved NHS costs, esp as a stroke resulting from AF is often more serious/disabilitating than stroke from non-AF cause. It would not change current pathway- just underpin in.	
		Expert #7 Yes, virtual palpitations pathways are being set up..	

		Patient history taken from referral and /or over the phone. Patient set up with device for a set period (1-3 months). ECG traces sent are interpreted by a Designated HCP qualified in ECG interpretation. Review is arranged once traces received and interpreted. Review often done by phone. This has reduced clinic attendances and reduced need to attend for holter fittings thus reducing footfall and social contact	
		Expert #8 Yes – absolutely on all those counts. Hence why I recommend usage of this device to my patients.	
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: Cost lest per item but as we use lots of them it does cost more overall given more devices and clinical physiology/ arrhythmia nurse time spend dealing with results. However it is expanding to meet the demands of the service.	
		Expert #2 It will cost less in capital terms, each device is currently £82.50 (plus VAT) compared to the price of an ambulatory monitor (circa over £1000). Staff still need to check incoming traces via email, this is currently completed by clinical investigations staff or arrhythmia nurses. This can be done from any care setting, including	

		working from home. Due to COVID restrictions on outpatient activity more and more outpatient activity will be completed remotely. Sending patients kardiamobile through the post or to be picked up locally in rural communities could offer significant health economy savings.	
		Expert #3 It is likely to save significant overall cost. Preventing 1 stroke saves thousands of pounds in the first year of care and subsequent years if the patient survives.	
		Expert #4 This would reduce time (KardiaMoblie is handheld, or for six-lead, both hands and one knee) and only takes 30 seconds to record. It does not require the patient to undress, or for multiple leads to be attached. It does not require much training to use, and patients have successfully used it to self-screen. The cost of a single KardiaMobile is significantly less than the purchase of a 12-lead ECG machine	
		Expert #5 Likely to cost less than current standard care. No associated ECG reporting costs. Device no more expensive that current standard care devices.	

		Expert #6 An AliveCor KM device costs around £90 (lead 1) and can be used for many patients. Takes about 5 mins for a nurse or doctor to learn to use it. This is in addition to standard care – but with savings to come in avoiding a patient having a stroke/associated home visits etc. Then the cost of confirmatory 12 lead ECG – usual service.	
		Expert #7 I expect it will be cost neutral or cost less as this technology will provide a rhythm strip during symptoms so even if ECG is normal patient can be reassured their symptoms are not caused by a dysrhythmia. This will reduce number of repeat holters and recurring referrals	
		Expert #8 Far less Patients - Earlier diagnosis, quicker intervention and hence better patient outcomes. Hospital – Earlier diagnosis, less repeated investigations, fewer hospital visits, ability to fit in with remote consultations and better patients outcomes and satisfaction.	
11		Expert #1:	

	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Same answer as above	
		Expert #2 We are currently researching this very question. We are comparing the diagnostic yield of kardiamobile compared to ambulatory monitoring. My feeling is that Kardiamobile will be a cheaper and more flexible alternative.	
		Expert #3 In the majority of cases it is being used as a screening tool. The resource impact is negative in purchasing the devices. Positive impact on resource is found all across the healthcare economy in paying for and treating fewer strokes. More AF detection will mean more 12 lead ECGs required and purchase of more stroke protection medication but models show that stroke protection medication demands considerably less resource that stroke treatment.	
		Expert #4 This is a difficult question, as it could increase diagnosis of AF, which would be more costly in terms of increased prescription of NOACS. On the other hand, all modelled cost-effectiveness studies suggest this will be cost-effective and in some scenarios cost-saving.	

		Expert #5 Likely to cost less than current standard care	
		Expert #6 As above	
		Expert #7 The staff resource should not change, those who interpreted holters can be assigned to Lead I interpretation. A palpitations service can be run from hospital out-patient setting or a community cardiology service	
		Expert #8 Less	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: Ensure there is a secure upload site, email currently for us	
		Expert #2 Clinical staff need to oversee interpretation of ECG traces. The devices automated software for identifying AF for instance is not accurate enough to be reliable. Clinical physiologists or nurses are the best and most cost-effective members of staff to be performing the ECG interpretation. Staff with a good understanding	

		of smartphone/tablet technology are also required to explain to the patient how to use KardiaMobile effectively.	
		Expert #3 The technology is fairly easy to use for healthcare professionals and has no implications on infrastructure. No training is required. It can be difficult for patients to use if not familiar with digital technology/smartphone/tablet use.	
		Expert #4 This requires less clinical facilities as there is no requirement for special rooms to take ECG, and can be done quickly and easily, reducing need for space to take 12-lead ECGs	
		Expert #5 Healthcare staff education required to instruct patients how to use device. NHS wifi needs to be suitable to allow app set up in hospital setting. There is the option to have a Kardia/AliveCor dashboard placed onto your hospital IT system to allow recorded patients ECGs to be viewed remotely. There are some IT challenges here. Data protection consideration with patients putting their identifiable information into the Kardia/AliveCor app. Kardia/AliveCor app also offers patient the opportunity to have ECGs	

		reported by a cardiologist for a fee which would not be required with an NHS adoption model and would therefore need to be removed or turned off.	
		Expert #6 As above- just minor addition to usual care – no extra facilities needed – unless clinician wants a standalone phone to receive patients' heart tracings.	
		Expert #7 Can be readily used in a cardiology team…. need admin and HCA to set patient up with device and HCP trained in ECG interpretation Dr, arrhythmia nurse, cardia physiologist.	
		Expert #8 Need infrastructure for data collection and data interpretation	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: Yes but not very complex nor time consuming for those used to looking at ECGs/ arrhythmias	

		Expert #2 A level of competent ECG interpretation is required. We use staff that have completed a healthcare science degree or nurses who have completed an ECG course run by the Society for Cardiological Science and Technology.	
		Expert #3 No, just a little practice.	
		Expert #4 Minimal training is required. The technology has been used successfully by a range of healthcare disciplines and by patients	
		Expert #5 Some simple training is required to educate patients and healthcare staff how to use device/app, and if required the Kardia/AliveCor dashboard.	
		Expert #6 5 mins on average- but in Staffs covered this in a best practice clinical update workshop; or in webinar demonstrating it from clinician & patient perspectives.	
		Expert #7 Infection control.. devices should be cleaned between use,	

		Confidentiality issues…. If using personal phone to use kardia , eg when pt is in clinic.. ECG should NOT be ID'd. ECG without patient details should be emailed directly to own email and then attached to the notes at time of recording. The ECG can then be identified once attached to the notes.	
		Expert #8 Yes – to analyse single lead ECGs	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: If patients can not use the device then we get no or poor quality recordings	
		Expert #2 Improper diagnosis of ECG traces is the main problem and particularly if atrial fibrillation is diagnosed from the device software without clinical input from someone with ECG interpretation knowledge. Patients have been anticoagulated inappropriately and not anticoagulated appropriately on the basis of KardiaMobile recordings although this is rare.	

		Several, the problem of incorrect diagnosis is discussed here: Mobile Health, Solution or Threat, Neth Heart J (2019) 27:16–17. Several examples of incorrect diagnosis of AF by clinicians relying on computer generated algorithms. Indication of a “normal” reading when actually an arrhythmia exists eg. Slow flutter	
		Expert #3 I am not aware of any adverse events or risks.	
		Expert #4 The technology presents no risk of harm when used appropriately. As with any reusable product there is a risk of cross-contamination if the device is not cleaned properly I am not aware of any adverse events There is a potential risk of false negatives and false positives, resulting in over- or under-diagnosis but the algorithms are highly sensitive and specific, so this risk is low. I cannot think of any theoretical adverse events that could occur	
		Expert #5	

		No known adverse risks.	
		Expert #6 From memory specificity & sensitivity rates are circa 96%. Thus potential harms are one in 25 chance of false reassurance. And for paroxysmal AF, patient may be reassured falsely if told heart rate normal with AliveCor screening & clinician does not describe that their AF may be on/off Nil adverse events observed,	
		Expert #7 Infection control…all devices cleaned between use. Identity of patient… ensure no one else has used it eg a child/relative Confidentiality issues when sending tracings and when stored on patient's notes.	
		Expert #8 False positive if data not analysed by appropriate personnel. But if clarification of ECG required patient can always have standard care investigations – this will be fairly rare in occurrence	
15		Expert #1:	

	Please list the key efficacy outcomes for this procedure/technology?	Can easily record and ECG when required	
		Expert #2 Ability to diagnose a range of arrhythmias using skilled clinician ECG interpretation	
		Expert #3 More cases of AF are being detected and more stroke prevention medication is being given.	
		Expert #4 Detection of abnormal heart rhythms in Lead I (Kardia single-lead) and Leads I, II, III, aVL, aVR, aVF (Kardia 6-lead)	
		Expert #5 Speed of diagnosis. A 'negative' finding of sinus rhythm/sinus tachycardia or ectopic beats during symptoms is as valuable as detection of a cardiac dysrhythmia as this will allow reassurance that the patient does not have a cardiac dysrhythmia as the cause of their palpitations. Reduction in investigations such as use of repeated unrewarding 24hr Holter monitors Reduction in healthcare usage for repeated attendances with undiagnosed palpitations as diagnosis made.	
		Expert #6	

		AF diagnosis confirmed by 12 lead ECG	
		Expert #7	
		Expert #8 Patients - Earlier diagnosis, quicker intervention and hence better patient outcomes. Hospital – Earlier diagnosis, less repeated investigations, fewer hospital visits, ability to fit in with remote consultations and better patients outcomes and satisfaction.	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: I have no concerns as long as we get a good quality recording we can make a diagnosis.	
		Expert #2 Clinicians relying on the computer generated potential diagnosis	
		Expert #3 None.	
		Expert #4 None known	
		Expert #5 IT issues will need some thought e.g. embedding symptomatic/diagnostic ECGs into	

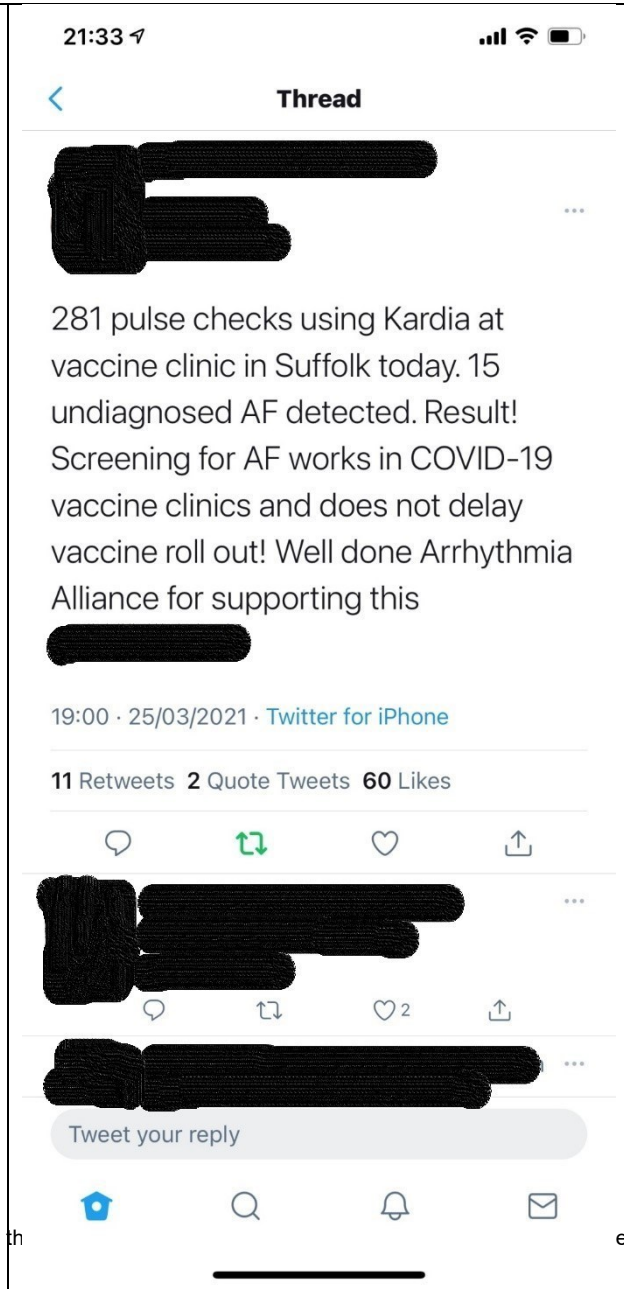
		the Electronic Patient Record, and having the Kardia/AliveCor dashboard placed onto the hospital IT system to allow recorded patients ECGs to be viewed remotely. ECG interpretation can occasionally be problematic when the recorded ECG included noise or artefact. Less experienced clinical staff may have difficulty interpreting the ECG and may be more likely to order additional investigations or further AliveCor wear time, whereas more senior clinicians (and those more comfortable with the technology) in our clinical experience seem to be more comfortable interpreting these recorded ECGs as normal sinus rhythm.	
		Expert #6 The sensitivity & specificity rates- as above	
		Expert #7	
		Expert #8 Nil	
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: Not in my view	
		Expert #2	

		Patients with access to smartphone/tablet technology are disadvantaged	
		Expert #3 I am not aware of any.	
		Expert #4 No	
		Expert #5 Whilst the Kardia/AliveCor doesn't seem from studies and our clinical experience to create a population of 'worried well' patients, this needs further work and evaluation. Need to ensure that those recording 'negative' finding of sinus rhythm/sinus tachycardia or ectopic beats during symptoms are reassured and do not continue to use healthcare resources despite the reassuring/benign diagnosis. No evidence of this in our research work but this does need further investigation.	
		Expert #6 Only the sensitivity & specificity rates- as above	
		Expert #7 Maintaining confidentiality when transferring tracing to patient notes and when used on HCP personal phone ; steps can be taken to ensure	

		the patient identity is not exposed or saved on HCP phone. Receive the tracings A secure nhs email is needed	
		Expert #8 Nil	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals. yes	
		Expert #2 Most or all district general hospitals. yes A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #3 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present. Unpredictable.	
		Expert #4	

		Most or all district general hospitals.- could be scaled anywhere. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK.	
		Expert #5 Most or all district general hospitals. Including community health settings (e.g. GP)	
		Expert #6 Most or all district general hospitals. & other NHS and social care settings	
		Expert #7 A minority of hospitals, but at least 10 in the UK. Will be mainly tertiary centres with arrhythmia service or community cardiology	
		Expert #8 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1: My arrhythmia nurse David Ferguson has already told you about a poster we submitted	
		Expert #2 Our own service explained via a poster presentation to the 2019 Heart Rhythm Congress: https://www.touchcardio.com/arrhythmia/journal-articles/137-the-introduction-of-a-smartphone-enabled-electrocardiograph-ecg-service-into-an-nhs-arrhythmia-service/ There are several studies looking at measuring QTc interval using the 6 lead version of kardia mobile in COVID 19 patients exposed to multiple QT prolonging drugs	
		Expert #3	



		Expert #4 AF Screen international consortium keeps a record of studies published by the group, some of which use Kardia https://www.afscreen.org/	
		Expert #5 Our one year experience of the Smartphone palpitation and pre-syncope ambulatory care Clinic (SPACC) service has been submitted to Annals of Emergency Medicine.	
		Expert #6 Ref cited above And our CVD/digital aids webinars- can send you link if you want	
		Expert #7 Affinity have some raw data on diagnostic yield using alivecor Not published but presented this at Heart Rhythm conference 4-5 years ago.	
		Expert #8	
20		Expert #1: Don’t know	

	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #2 Many hospitals and AF detect, protect, perfect projects are publishing the results of their trials	
		Expert #3	
		Expert #4 There are many ongoing studies,. The one we are waiting for is this one- using zenicor, but prospectively tests if screening with a single-lead ECG genuinely reduces strokes https://www.safer.phpc.cam.ac.uk/	
		Expert #5 Not aware	
		Expert #6 Don't know	
		Expert #7 Not aware	
		Expert #8	
21	Approximately how many people each year would be eligible for an intervention with this	Expert #1: 80+ % if they have a compatible mobile phone	

	procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #2 All patients with symptomatic arrhythmias who have access to smartphone/tablet technology. All patients with a diagnosis of stroke with access to smartphone/tablet technology.	
		Expert #3 The UK population is around 65 million. AF is thought to be known in around 1% of the population and undetected in a further 1%. National screening has been considered and narrowly rejected. Opportunistic screening is advocated. Devices like this are likely to help us pick up the potential 650,000 undetected AF cases to prevent many avoidable strokes. (all approximate figures)	
		Expert #4 Adults over 65 years (approx. 11.9 million)	
		Expert #5 Patients with palpitations and pre-syncope commonly present to Emergency Departments, accounting for 300,000 ED presentations a year in the United Kingdom and being one of the commonest presentations to general and family practice (16% of presentations).	

		1. Thiruganasambandamoorthy, V.; Stiell, I.G.; Wells, G.A.; Vaidyanathan A; Mukarram M; Taljaard, M. Outcomes in Presyncope Patients: A Prospective Cohort Study. Ann. Emerg. Med. 2015, 65, 268–276.e6. 2. Probst, M.A.; Mower, W.R.; Kanzaria, H.K., Hoffman J.R.; Buch E.F.; Sun B.C. Analysis of emergency department visits for palpitations (from the National Hospital Ambulatory Medical Care Survey). Am. J. Cardiol. 2014, 113, 1685–1690. 3. Raviele, A.; Giada, F.; Bergfeldt, L.; Blanc, J.J.; Blomstrom-Lundqvist, C.; Mont, L.; Morgan, J.M.; Raatikainen, M.P.; Steinbeck, G.; Viskin, S.; et al. Management of patients with palpitations: A position paper from the European Heart Rhythm Association. Europace 2011, 13, 920–934, doi:10.1093/europace/eur130. I am not aware of the similar primary and secondary stroke and TIA prevention data.	
		Expert #6 10% of adults>60 years?	
		Expert #7 Approx 80% target population	
		Expert #8	

		50% of target population at least	

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 If they have not got or can not use a mobile phone or tablet then it is no use	
		Expert#2 Yes, users need a degree of computer or smartphone literacy to be able to use the device effectively	
		Expert#3 As it needs to be linked to a smartphone or tablet, there is the potential for digital exclusion. AF is far more common in advancing age and so is digital exclusion so the younger AF patients would benefit more in personal use. When used for AF detection by health care professionals this evens out.	
		Expert #4 Has to be paired with a device- usually a mobile phone. Needs an adequate wifi signal. Problematic if thick walls in the area in which ECG is being recorded.This can be overcome by switching the phone into airplane mode. Difficult if patient has a strong tremor.	
		Expert #5 Covered above	
		Expert #6 Not that I know of	
		Expert #7	

		Has to be smart phone compatible. Convenience …some say unable to get phone out if working Some of elderly population have poor dexterity	
		Expert #8 How is the device to be funded and if funded by NHS need robust way to ensure the small device is returned to NHS by patient.	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 none	
		Expert#2 Funding considerations are the main barrier and finding time for appropriate analysis of ECG rhythm strips by appropriately qualified staff.	
		Expert#3 No. It is used widely in the NHS.	
		Expert #4 Good linkage of data, concerns about where data is stored and if it is compliant. Needs to be embedded as part of a clear clinical pathway	
		Expert #5 Covered above	
		Expert #6 None known – just getting clinicians thinking they've time to learn to adopt new technology	

		Expert #7 Cost and resource to support its use eg, trained staff to interpret tracings,	
		Expert #8 No	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 More data confirming its use and cases identified	
		Expert#2 I think the research base is large enough now for the technology to be used, research as to how much it costs compared to the NHS tariff for ECG monitoring would be interesting.	
		Expert#3 No.	
		Expert #4 As detailed previously, confirmation that early detection of AF prevents stroke is desirable and this evidence is currently being generated	
		Expert #5 Covered above	
		Expert #6 Just good to know latest on sensitivity & specificity rates between AliveCor lead 1s and lead 6s – might already exist.	

		Expert #7	
		Expert #8	
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#1 Beneficial outcome measures: Numbers of patients with any arrhythmia identified Treatment plans changed as a result of their use Adverse outcome measures: Poor quality recordings that have no use	
		Expert#2 Beneficial outcome measures: Less visits by patients to primary and secondary care premises. Cost of arrhythmia diagnosis compared to ambulatory ECG monitoring	

		Adverse outcome measures: The number of incorrect diagnoses of AF and other arrhythmias	
		Expert#3 Beneficial outcome measures: It would be easy to audit thie device v standard practice to see if there is more AF detection. Adverse outcome measures: Unaware.	
		Expert #4 Beneficial outcome measures: AF detection rates at single time point or over time CHA2DS2VASc scores in identified population % of patients who have an effective treatment plan commenced as a result of detection Adverse outcome measures: N/A	

		Expert #5 Outcome measures: Cost of diagnosis Palpitations: 1) Speed of diagnosis of a clinical symptom/ECG rhythm correlation. 2) Reduction in investigations such as use of repeated 24hr Holter monitors 3) Healthcare usage (e.g. repeated attendances with undiagnosed palpitations/ reduction in investigations) 4) Patient satisfaction measures 5) Reduction in patient anxiety associated with undiagnosed palpitations Primary and secondary AF detection in TIA/CVA patients: 1) Reduction in undiagnosed AF 2) Reduction in TIA/CVA rate	
		Expert #6 Beneficial outcome measures: Diagnosed AF/ confirmed by 12 lead ECG Subsequent anticoagulation if AF confirmed.	

		Adverse outcome measures: Someone with paroxysmal AF not detected to have AF when used AliveCor device for 30 seconds; and falsely reassured.	
		Expert #7 Beneficial outcome measures: Suggest over a 6 month period Ease of use for pt Quality of rhythm strip Percentage of sinus rhythm captured Percentage of AF captured Percentage of other dysrhythmia captured Percentage of SR with ectopics. Time scale between receiving device and diagnosis Number of unreadable tracings	

		Adverse outcome measures:	
		Expert #8 Beneficial outcome measures: Time to diagnosis - months Strokes prevented – over 1 year compared with standard care PROMS over 1 year Adverse outcome measures: False positives rate and impact on PROMS Need to resort to standard of care	
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 It is a great device and has allowed many more patients to be investigated and diagnosed or reassured.	

		Expert# 2 I am convinced that the use of kardiamobile together with other lead one ECG monitors is a useful progression in arrhythmia detection. Resources should be steered towards less hospital visits for patients and this together with other technology can help. Primary care need incentives to use it appropriately and costings need to be accurately calculated in comparison to current NHS tariffs.	
		Expert#3 I find them useful and easy to use in the intended manner. I use them regularly for my patients and get useful results	
		Expert #4 I have worked in AF detection for approximately 11 years. I have conducted a number of studies using Kardia single lead ECG to detect AF.	
		Expert #5	
		Expert #6 Should be adopted at scale as usual service in all NHS settings.	

		Expert #7 Effective at capturing dysrhythmia during symptoms and if irregular pulse detected. Education and good user use will enhance quality of trace. Sometimes tracings unreadable Device sometimes stops working ... often requires new battery . can be tricky changing battery We found, many of elderly population didn't have compatible phone and some unable to coordinate its use. When set up correctly and user shown how to gain best trace, this is a very effective tool to capture dysrhythmias. As a HCP, is useful to have this to hand during consultations, if irregular pulse identified	
		Expert #8	

Appendix 6

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Engagement Meeting

GID-MT554 KardiaMobile

NOTES

Date: **7 May 2021**

Time: **14:00 to 15:30**

Documents

MIB: https://www.nice.org.uk/advice/mib232

MTG Scope: https://www.nice.org.uk/guidance/indevelopment/gid-mt554/documents

In Attendance

NICE: Chris Chesters (CC), Lizzy Latimer (LL), Ying-Ying Wang (YYW), Dionne Bowie (DB)

Newcastle EAC: Andrew Sims (AJS), Kim Keltie (KK), Rachel O'Leary (RO), Emma Belilios (EB), Kathryn Fletcher (KF)

AliveCor: Sean Warren (SW), Stefan Holzer (SH)

Device Access UK: Michael Branagan-Harris (MBH), Debbie Postlethwaite (DP),

Optimax Access Ltd: Mehdi Javanbakht (MJ), Amir Ansaripoor (AA)

NOTES

Welcome and introductions

LL led introductions and noted that the aim of company engagement meetings is to provide an opportunity to discuss any matters associated with the submission that have not been resolved through routine correspondence.

EAC Evidence Review

Clinical Evidence

KK noted that the write up of the assessment of the Company's clinical submission is complete, the evidence has been reviewed and appraised.

- Summary narrative is complex due to heterogeneity in studies (different populations, settings, study types, comparators, across a large number of outcomes).
- This makes it difficult to unequivocally confirm each benefit of KardiaMobile (although the EAC would consider, in general, the benefits claimed by the Company are plausible).
- There do not appear to any major safety issues with the device, and ease of patient use is reported consistently in the published evidence.
- The EAC would therefore consider that, on the basis of the clinical evidence, KardiaMobile should be considered as an available option to support diagnosis and monitoring of AF.
- The EAC is uncertain of KardiaMobile's place in the clinical pathway, particularly as the IFU state that the output alone cannot be used for a clinical diagnosis.
- Therefore clinical interpretation of the KardiaMobile output is required (thus false negatives and false positives from the device are not considered a major safety issue), and the workflow of the device and the Kardia app in the NHS is not yet clear.

Economic Evidence

EAC has critically appraised the published economic evidence, and has begun appraisal of the de novo model submitted.

Usually the EAC's first step is to replicate the Company base-case, however due to the complexity of the model this has not yet been possible

The model is complex, the description is not transparent, and the assumptions and structure of the economic model do not reflect the clinical evidence. For example:

- Zio (patch) and implantable cardiac recorders have been included as comparators, however there was no direct comparison of these to KardiaMobile in the evidence submission.
- Model extends to 5 years, however there was no direct evidence of reduction in strokes long-term in the clinical submission associated with use of Kardia Mobile.

- No clinical time for KardiaMobile ECG review has been included (despite diagnostic accuracy studies including this, and IFU).

Discussion about the issues raised in the Expert Engagement Meeting

LL shared clinical expert feedback from the Expert Engagement meeting. Company will see full notes from the call when the correspondence log is published.

i) **Experts reported that background noise when taking a trace using a mobile device can cause interference**.

Response: SW and SH clarified that the transmission method differs between the single lead and 6-lead devices. The single lead device uses high frequency acoustic ultrasound (~19 kHz) and the phone's microphone. The company confirmed that background noise would not impact the Kardia app classification (e.g. "normal", "possible AF") however it can stop the transmission of the trace from device to phone. The IFU recommends that patients take measurements in a quiet environment. This is not an issue with the 6-lead device which uses Bluetooth. Multiple Bluetooth devices in close proximity could potentially cause interference with transmission (e.g. at conferences with hundreds of devices), but the Company thought this was unlikely in normal clinical use. Interference from devices running at the same frequency could cause an unreadable result. Finger dexterity (tremor) is more likely to be the cause of an unreadable trace (noise) than electrical interference. The device identifies electrical interference, stops the ECG trace and instructs the patient to take another recording. Company reported that the feedback they have from patients is that interference is not a significant problem. The company provides instructions on how to record a stable ECG on their website.

ii) **Experts reported compatibility issues e.g. software upgrade on phone meant Kardia app stopped working, or Kardia app upgrade meant no longer worked on same phone**.

Response: The list of compatible devices was listed in the MIB, however the Company will provide the list of devices which are compatible with KardiaMobile. All Kardia app updates are checked against this list. KardiaMobile may work on other devices, although upgrades to the app and phone upgrades can interfere with this. The company stated it could not guarantee the security and functionality of KardioMobile on devices that were not listed as compatible. The Company suggested that it would be helpful if the NHS had a

standardised list of devices as well, to ensure compatibility with the most common devices. The Company ask customers to contact their helpline if a device identified as compatible stops supporting use of KardiaMobile so they can rectify the situation.

iii) **Experts reported concern over data security**. One expert reported that they set up the app for their patients in clinic using non-identifiable 'dummy' data to protect their personal data.

Response: The Company (SH) confirmed this is not an issue. They consider that the system is fully compliant with GDPR legislation but will work with dummy data if people are concerned. Only issue is if the user does not give a real email address and they forget their password they cannot be sent a reminder.

The AHSNs distributed c.6,000 KardiaMobile devices to GPs for support of single-time point testing. GPs were advised to register with their own details and then to set up their patients as anonymous guests. Single-time point testing is out of scope for the AR, but the advice might have come from this scenario. The device will usually pick up if someone other than the registered person is using it. The scope for this assessment assumes the device is registered to the individual using it. The ECG trace also contains the patient information (so that the clinician knows who the trace is from, for accurate record keeping), and if dummy data was entered then the clinician would only have the email address of the person sending the trace to them. In all, the company confirmed that email address and ECG trace are identifiable data for individual patient.

SW agreed to outline the data flow pathway in an email for discussion on a separate call with the EAC. This will also be helpful to the Committee.

Questions on the economic evidence submission

Next steps

- Company will provide written responses to the EAC's questions on the economic evidence submission by Mon/Tuesday next week (10/11 May 2021)
- SW will liaise with KK to arrange a call week commencing 10 May 2021 (AJS, KK, SW, MJ and AA) to discuss outstanding queries regarding the model. LL confirmed there is no limit on how many

times the EAC and the Company can meet to discuss the model other than the constraints of the project timeline. However all correspondence will be documented and added to the correspondence log which will go in the public domain.

- SW will outline the data flow (user scenarios) for discussion on the call.
- SW will send list of compatible devices.
- The EAC will circulate notes from this call for review by all attendees. Once the notes are accepted as an accurate record of the call they will be added to the correspondence log which will be published on NICE's website. The Company are asked to highlight any commercially sensitive or academic in confidence material for redaction.
- SW will update on DTAC process as soon as he can.
- The Company noted that the company's model is confidential and should be redacted. LL will check if this is an issue as NICE processes require an executable version of the model to be made available on request during consultation.

Questions on the economic evidence submission

The Company will also give written response (10th/11th May).

General questions for AliveCor

1. Has the Kardia app been assessed against the Digital Technology Assessment Criteria (DTAC)?

   Response: Company have been invited by NHSX to complete DTAC submission, SW is in the process of completing the submission. Hoping to complete by the end of the month depending on certification requirements. Will share the outcome when received.

2. The write up and Excel model are extremely complex. Previously the company had described the model as a decision tree leading into a Markov model. However the submitted model looks like a 100-day diagnostic Markov model (with a daily cycle) leading into a 5-year management Markov model (with a yearly cycle). Why was this approach taken?

   Response: The model had to be complex to accommodate time-dependent probabilities in the diagnosis phase. A key benefit of KardiaMobile is that the patient can email a trace that has been determined by the algorithm to be "possible AF" to their clinician for interpretation. This immediate patient feedback is not possible with Holter monitor, or Zio patch. This means diagnosis can be confirmed and treatment can be started as quickly as possible. The algorithm has a high negative predictive value, so the base-case model assumes only clinical review of positive results and no further investigation is needed for a negative result (although the model can run any scenario, including clinical review of all traces). However, the EAC highlighted that the instructions for use (IFU) state that the output classification cannot be used for clinical diagnosis, and therefore all traces should be reviewed by a clinician.

   The Company are happy to work with the EAC to make sure they have the information they need to make the model usable. MJ and AA will provide full written answers to the questions on the model and are happy to participate in a follow up meeting to walk through the model and address any outstanding uncertainties. SW will contact EAC directly to arrange the meeting.

   The device supports patients with self-management. Clinicians would guide patients on how to do this. Patients might be instructed to take a trace when

they are symptomatic and share any traces that are positive for AF. All traces will be stored on the patient's mobile device so clinician can review them when the patient comes into clinic.

The main comparator is a Holter monitor - this monitors continuously for a fixed time (e.g. 24 hours). KardiaMobile has no limit, can monitor continuously for as long as needed, however in the model, a limit of 14 days has been assumed (MJ clarified that this can be altered up to 28 days). The justification given for this was that in the Hermans et al. (2021) study, all AF patients were detected within 14 days. However, the EAC pointed out that Hermans was looking at AF recurrence in patients post-ablation.

3. The company has included Holter monitor (7 days), and Zio patch (14 days) as formal comparators. However, the costs of Holter (24h, 48h), continuous event monitoring (30 days), and implantable cardiac monitors have been included within repeat testing. Can you explain why these have been introduced (but not included as formal comparators)?

   Response: Several different comparators can be selected in the model. The Company confirmed that there is no published evidence comparing Zio or implantable monitors with KardiaMobile. The data source of the comparison between Holter and Kardia is based on Hermans et al (2021).

   The model uses inputs from published evidence on the diagnostic accuracy of Zio and patch monitor. Different sensitivity and specificity can be defined for different comparators. KK noted that the diagnostic accuracy reported in the Hermans study was based on per ECG recording, and questioned what assumptions were used to convert from "per ECG recording" sensitivity and specificity to "per patient" sensitivity and specificity, as none of the clinical evidence reported per-patient 2x2 diagnostic accuracy tables. Depending on the performance of the test, the number of further tests needed and the proportion of people needing repeat tests may vary. Multiple ECGs from the same patient are not independent of each other; repeated testing will cause sensitivity to tend towards 100% and specificity to tend towards 0%.

4. Given that implantable devices are typically used long-term (battery life between 2-5 years), repeated monitoring with one would take longer than the 100 days diagnosis in the model – can you explain why this was included?

   Response: Any of these tests may be used for patients needing repeat testing if there is still no diagnosis after 24-hour Holter monitor followed by 48-hour Holter monitor. Clinicians would prefer to go with less invasive options before considering an implantable device. The Company took expert advice

on testing options. The model allows the user to set probability to zero for any of the comparator tests.

From the IFU, patients with implantable cardiac devices (ICDs) would be contraindicated for KardiaMobile. Due to this, KK queried whether those requiring an implantable cardiac monitor were a different population.

5. We have not identified any studies directly comparing KardiaMobile to Zio, CER or implantable cardiac monitoring; can you confirm this evidence was not included in the clinical submission?

   Response: Company confirmed they are not aware of any studies directly comparing KardiaMobile with Zio or implantable cardiac monitoring.

6. Continuous event monitoring is included in the model, but not explicitly described in the narrative. Can you describe what this arm entails please?

   Response: Not discussed on the call

7. The model includes a 5-year Markov model looking at the management of AF, yet there was no direct long-term evidence for reduction in strokes in the clinical submission. Please would you clarify what assumptions have been made to link the diagnostic performance of Kardia Mobile to this outcome?

8. **Response**: KardiaMobile speeds up AF diagnosis. As a result, patients receive medication and according to different studies, patients on treatment have a lower likelihood of stroke compared to undiagnosed AF. Therefore, we can expect less stroke and death associate with stroke in patients used KardiaMobile. The EAC commented that there is no direct evidence to support this in the literature.

   Response: Not discussed on the call

9. You have assumed that all monitoring tests with Holter, Zio or CER would be followed up with a clinic visit regardless of findings, based on MTG52. However, MTG52 states in point 4.9, "Comments and clinical expert advice received at consultation suggested that an outpatient appointment would normally only be needed after a significant positive result, regardless of the ECG monitoring device used. " Can you explain how you arrived at this assumption? Why is KardiaMobile not followed up with a clinic visit?

   Response: Have assumed only AF positive cases will need to be seen in clinic, but the EAC can adjust this in the model. KK highlighted that the base case goes against the device IFU.

10. Age (64 year) and gender (55% male) is included in the model. Can you confirm that both age and gender are only used to determine risk of death at each cycle? (i.e. can you confirm that age and gender are not used to determine risk of AF, or risk of stroke)?

    Response: The Company confirmed age and gender are only used to determine risk of death.

    AJS asked how the assumption of prevalence of AF changes as patients move through the pathway and how does the model reflect this?

    AA clarified that confirmed AF cases would not undergo further monitoring as the model assumes 100% sensitivity for clinician decisions. Those who undergo repeat monitoring are a mixture of undiagnosed and no AF cases. As the model cannot estimate the proportion of undiagnosed and no AF cases in repeat monitoring, it assumes the same prevalence in the repeated cases, which would be the case for a relatively small proportion of patientsAA stated that the same assumptions were made in the Zio MTG. AF prevalence can be altered in the model to explore different scenarios.

11. The model includes a 2-year life-span in KardiaMobile device costs – however it is only used for 14 days within diagnosis phase. Length of device use in literature (Clinical Submission) is much longer; the diagnostic accuracy study by Hermans et al (2021) used KardiaMobile for 4 weeks, Javed et al. used for median of 20 months. Can you explain why 14 days was used?

    Response: Answer in response to Question 2.

12. The model structure (Appendix B) indicates that cases categorised as AF by KardiaMobile, which are then reviewed by clinician and regarded as a false positive (i.e. not AF), require repeat testing? Is this correct?

    Response: Not discussed on the call

13. KardiaMobile followed by clinician interpretation which does not detect AF is regarded as “not AF”. However, Holter monitoring followed by clinical interpretation which does not identify AF is regarded as “inconclusive” – and subjected to repeat monitoring. Why the different approach for the comparator arm?

    Response: Not discussed on the call

14. The economic submission states that there is a maximum of 2 repeated diagnostic tests, however “HOLTER” worksheet looks as though 3 repeat tests have been included (Column R). Can you explain?

    Response: Not discussed on the call

15. The summary states that cost savings are largely driven by reduction in number of health care visits. The cost of KardiaMobile ECG review has not been included in the technology costs; however, the IFU states that KardiaMobile cannot be used for clinical diagnosis without clinical interpretation. Can you explain why this has not been included in the model?

    Response: Not discussed on the call

16. Cost of GP visit was based on per patient contact of 9.22 minutes.

    a. No reference for this number is provided. Where did this number come from?

    b. GP visits are not included in base-case (column CI in “KM”, “HOLTER” and “Zio” worksheets). Therefore, why has it been included in the executable model?

    Response: Not discussed on the call

17. The model includes QALYs and ICER however these are not normally considered within MTEP processes (which focuses on cost consequence). Can you explain why these have been included?

    Response: Not discussed on the call

18. Transition probabilities: probability of true AF positive (KardiaMobile) = 1.00, but probability of true AF positive (KardiaMobile and clinician) = 0.77 – can you explain please?

    Response: Not discussed on the call

19. The cost of KardiaMobile is listed as £82.50 – but the breakdown is not stated. Is this an average cost of the single and 6-lead KardiaMobile Heart Monitor? Is the Kardia app free of charge?

    Response: Single lead device costs £82.50 (excl VAT), 6-lead device costs were not included in the model: £124.20 (excl VAT). Confirmed Kardia app is free of charge.

20. Technology cost of KardiaMobile is listed as £82.50 per device, but £8.96 per monitoring session is inserted into the model we assume to account for the device being reusable. [This is based on 2 year life of device and 14 days monitoring with KardiaMobile with 5 days between patients; (2*365)/(14+5) = 38 uses in device lifetime, and a total cost of £344.25]. Device breakage/loss and battery not included. Can you explain?

    Response: Company confirmed that the battery is included in the cost (replacement battery is not).

    Very long-term monitoring is unlikely for patients in scope for this AR, 2 weeks likely to be long enough for detecting AF. KK commented that this is why the EAC is querying the inclusion of implantable cardiac monitors in the comparator arm.

21. The costs sourced from Zio (MTG52) state “inflated to 2019”. However, MTG was published in 2020 and consumer price index to inflate 2020 to 2021 is not available from ONS yet. Inflation of 1.0183 appears to have been applied. Can you explain the inflation?

    Response: Not discussed on the call

22. The submission states that “initial inconclusive results from the device may also undergo subsequent clinical assessment”. Does this mean unclassified readings? Or unreadable readings? Or both combined? From some of the calculations this includes “normal sinus” outcomes – however this seems counterintuitive?

    Response: Not discussed on the call

23. Clinical parameters (Table 3) state a waiting time for diagnosis with Zio of 3 (2-5) days sourced from Kaura et al. 2019. However, this study randomised patients with previous stroke/TIA to either standard care (Holter monitoring, approx. 24 hours) or patch-based monitoring (Zio patch, 14 days). Primary outcome was detection of AF lasting at least 30 seconds within 90 days. This study does not report waiting time for diagnosis; therefore it is unclear where the company obtained these values?

    Response: Not discussed on the call

24. “Inter calculations” worksheet appears to use the per-recording diagnostic accuracy of KardiaMobile and KardiaMobile+clinician interpretation (excluding results “unreadable” on KardiaMobile) and converts into a per-patient proportion. The breakdown per-patient was not reported in Hermans et al.

2021, and the approach taken is not explained explicitly in the spreadsheet, therefore can you explain your calculations and approach?

Response: Not discussed on the call

25. In MTG52 (Zio), the EAC estimated a mean of 1.465 additional tests were required for the group of patients requiring test repetition. Can you confirm cell D85 in “Inter calculations” worksheet is a typo (i.e. 2.465)? Does this impact cell D76 also?

    Response: Not discussed on the call

26. Following the clinical pathway (Section 3 of Clinical Submission), patients with irregular pulse from manual pulse palpation would undergo 12-lead ECG. 12-lead ECG would capture all cases of persistent AF. Therefore can you provide the basis of the assumption of 30.3% prevalence of AF used in the model?

    Response: Not discussed on the call

27. Cost of NOACs (daily) in the model is listed as £1.91. Can you share the exact reference used? And whether a weighted average was used?

    Response: Some costs came from the Zio evaluation (MTG52). This was published 2019/20, but costs were from 2017/18 so have inflated this. MJ will provide the exact link to where NOACs came from (including page number).

28. Cost of stroke (first/subsequent years), major bleed, intracranial haemorrhage, MI are referenced to TA607. Can you please state exactly where in TA607 these costs come from? The reference to TA607 states that costs were inflated to 2019 prices, however TA607 was published in 2019, therefore can you please share any inflation applied.

    Response: MJ will provide the exact link to where cost came from (including page number).

29. Cost of fatal event (£2258) references Walker et al. 2016. Can you please share where you obtained this cost and any inflation applied?

    Response: MJ will provide the exact link to where cost came from (including page number).

30. At the end of the diagnosis phase the following states are populated:

    a. Can you explain why Zio has fewer diagnosed with AF than Holter?

b. Can you also explain why diagnosis of AF starts populating from day 1 in KardiaMobile arm (and not day 4 like the Holter monitor arm? Both have 3 day wait time for diagnosis from the inputs of the model?)

c. Can you also explain who is in the "undiagnosed AF" group – particularly for KardiaMobile which has gone through the app, and been reviewed by a clinician?

	Diagnosed AF	**Undiagnosed AF**	**No AF**	**Dead**
KardiaMobile	25.8% (starts from day 1)	4.5%	69.4%	0.3%
Holter	17.6% (starts from day 4)	12.7%	69.4%	0.3%
Zio	16.6% (starts from day 17)	13.8%	69.4%	0.3%

Response: Not discussed on the call

Appendix 7

Company Engagement Meeting (07/05/2021)

General questions for AliveCor

31. Has the Kardia app been assessed against the Digital Technology Assessment Criteria (DTAC)?

Response: This is in process now as we are finalising ISO27001 and other requirements from the assessment, following an invitation from NHSX.

32. The write up and Excel model are extremely complex. Previously the company had described the model as a decision tree leading into a Markov model. However the submitted model looks like a 100-day diagnostic Markov model (with a daily cycle) leading into a 5-year management Markov model (with a yearly cycle). Why was this approach taken?

Response: Please accept our sincere apologies if the model looks too complex. One important aspect of KardiaMobile's capability compared to other comparators, is the possibility of rapid diagnosis using mobile app features (forwarding the results to a clinician immediately after a positive AF detection). We wanted to develop the model to capture this capability, while considering the point that most AF detections happen in the first days of monitoring (according to Hermans et al, 2021). Moreover, according to the published scope by NICE, we wanted to develop the model in a way that will enable us to run scenarios in which different numbers and combinations of devices are needed. Therefore, the model complexity came from a combination of us needing to incorporate time-dependent probabilities, and to capture a combination of various monitoring devices for the detection of AF.

33. The company has included Holter (7 days), and Zio patch (14 days) as formal comparators. However the costs of Holter (24h, 48h), continuous event monitoring (30 days), and implantable cardiac monitors have been included within repeat testing. Can you explain why these have been introduced (but not included as formal comparators)?

Response: All types of Holter can be considered as a primary comparator; you just need to select one of them using the dropdown list in the "Results" sheet, cell H5. Longer AF monitoring procedures (continuous event monitoring (CER) and implantable cardiac monitors (LR)) were considered as the second line of monitoring, because these procedures are not used in practice as the first line of AF monitoring. This is according to clinical expert opinion and is consistent with the previous NICE submission for Zio (MTG52). Additionally, the patient pathways suggest implantable event recorders are not standard of care and are only used as second- or third-line tests when other methods of ECG ambulatory monitoring have failed to diagnose or rule out arrhythmia.

34. Given that implantable devices are typically used long-term (battery life between 2-5 years), repeated monitoring with one would take longer than the 100 days diagnosis in the model – can you explain why this was included?

Response: We have mainly modelled the diagnostic performance of KardiaMobile and the direct comparators (i.e. Zio and Holter) and based on the clinical evidence for KardiaMobile (Hermans et al) and the direct comparators we felt that 100 days would be sufficient. implantable devices are used in the third round of AF monitoring with the model capturing their associated costs and not their AF detection rate. It is worth noting that only a very small proportion of cases will need

to use them. This approach is similar to the Zio Submission where a one year time horizon was used for the economic model. We know that one year also is not sufficient to capture long-term impact of expensive loop recorders.

35. We have not identified any studies directly comparing KardiaMobile to Zio, CER, or implantable cardiac monitoring; can you confirm this evidence was not included in the clinical submission?

Response: We did not identify any studies directly comparing KardiaMobile to Zio, CER, or implantable cardiac monitoring in the systematic review of clinical evidence.

36. Continuous event monitoring is included in the model, but not explicitly described in the narrative. Can you describe what this arm entails please?

Response: Continuous event monitoring (CER) is used as the second- or third-line of monitoring when the direct comparators (i.e., Zio, Holter 24h, 48h, and 7 days) have failed to diagnose or rule out arrhythmia. The user can select the percentage of time that CER will be used after the direct comparators failed to diagnose or rule out arrhythmia. Please see cell F92 and F99 on the "USER INPUTS" page in the model.

37. The model includes a 5-year long-term Markov model, yet there was no direct long-term evidence for reduction in strokes in the clinical submission. Please would you clarify what assumptions have been made to link the diagnostic performance of Kardia Mobile to this outcome?

Response: The rate of stroke depends on how quickly patients could be diagnosed and start preventive medicine. Given that patients who use KM can be diagnosed and referred for treatment faster than those patients monitored using alternative methods, rapid AF detection using KM would result in quicker treatment initiation and a lower stroke rate compared to undiagnosed AF.

38. The model includes an absorbing state (death); however, there was no direct evidence linking Kardia Mobile with avoidance of deaths in the clinical submission. Please would you clarify what assumptions have been made to link the diagnostic performance of Kardia Mobile to this outcome?

Response: The model captures age-specific background mortality, and mortality due to AF complications such as stroke. As in the previous response, quicker AF detection may result in reduced complications and consequently a lower mortality rate. Therefore, it is the ability of KM to lead to quicker diagnosis of AF, and more rapid initiation of treatment, that impacts the associated mortality rate compared to alternative technologies.

Specific economic model questions for AliveCor:

39. You have assumed that all monitoring tests with Holter, Zio, or CER would be followed up with a clinic visit regardless of findings, based on MTG52. However, MTG52 states in point 4.9, "Comments and clinical expert advice received at consultation suggested that an outpatient appointment would normally only be needed after a significant positive result, regardless of the ECG monitoring device used. " Can you explain how you arrived at this assumption? Why is KardiaMobile not followed up with a clinic visit?

Response: We couldn't identify point 4.9. But what we used was based on the below statement from MTG52 (page 95 of 744):

https://www.nice.org.uk/guidance/mtg52/documents/supporting-documentation-2

than once (but less than twice on average).

The EAC regarded the stroke model as acceptable. The EAC thought that an outpatient visit would be required regardless of the outcome of any test.

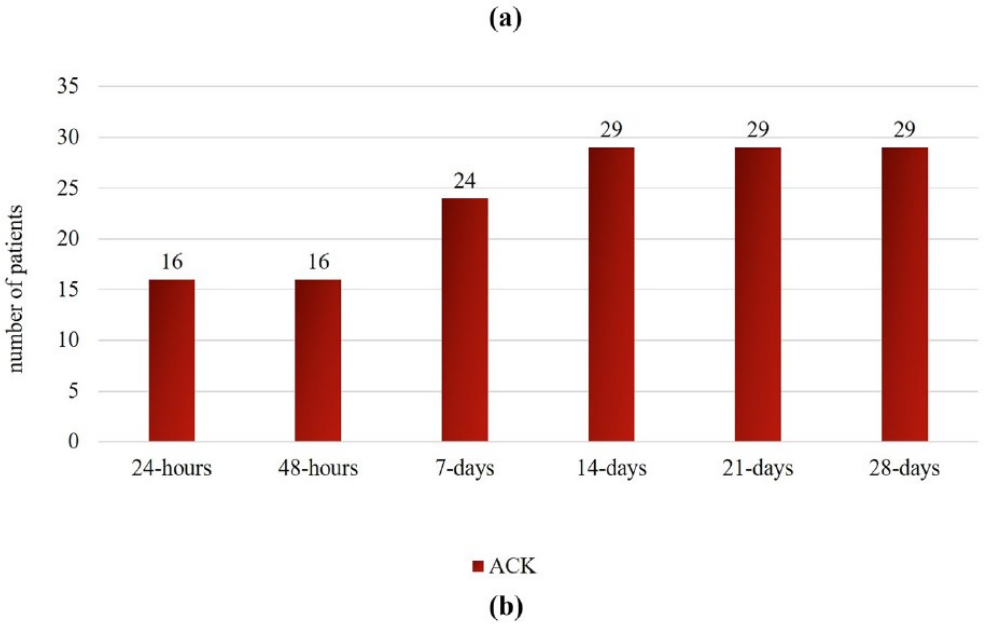
Downstream stroke model

40. Age (64 year) and gender (55% male) is included in the model. Can you confirm that both age and gender are only used to determine risk of death at each cycle? (i.e. can you confirm that age and gender are not used to determine risk of AF, or risk of stroke)?

Response: Yes, age and gender are only used to determine risk of death at each cycle.

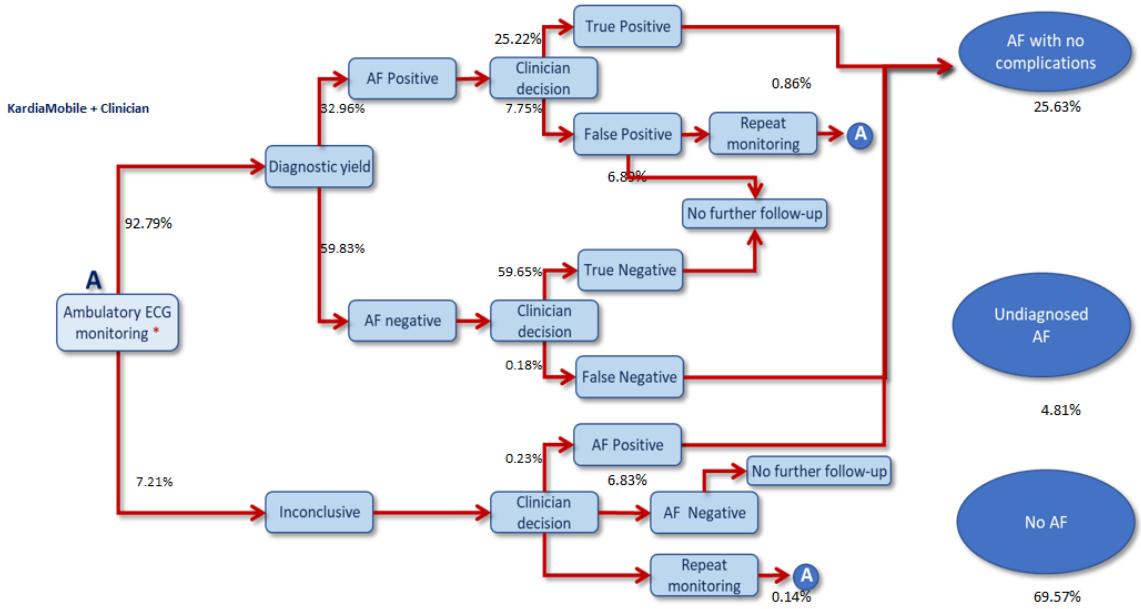
41. The model includes a 2 year life-span in KardiaMobile device costs – however it is only used for 14 days within diagnosis phase. Length of device use in literature (Clinical Submision) is much longer; the diagnostic accuracy study by Hermans et al (2021) used KardiaMobile for 4 weeks, Javed et al. used for median of 20 months. Can you explain why 14 days was used?

Response: This is based on the clinical study (Hermans et al, 2021) that is used to inform the model. The Hermans paper and others indicate that a diagnosis is identified within 14 days of using KM, however there is no limit to its usage. Based on the study by Hermans et al, 2021, more than 14 days of long-term intermittent heart rhythm monitoring did not increase the detection rate of recurrent AF, suggesting that 14 days may represent a sufficient monitoring time for intermittent heart rhythm follow-up.



42. The model structure (Appendix B) indicates that cases categorised as AF by KardiaMobile, which are then reviewed by clinician and regarded as a false positive (i.e. not AF), require repeat testing? Is this correct?

Response: This is not correct. Only a very small proportion of AF false positive (0.86% out of 7.75%) are candidates for repeat testing.



43. KardiaMobile followed by clinician interpretation which does not detect AF is regarded as "not AF". However Holter monitoring followed by clinical interpretation which does not identify AF is regarded as "inconclusive" – and subjected to repeat monitoring. Why the different approach for the comparator arm?

Response: We used this approach to keep the model structure identical in all arms. This does not mean a different approach for the comparator arms. Unlike with KM, the Holter and Zio devices cannot give any diagnosis; therefore, based on the clinical evidence for Zio and Holter, diagnostic yield value is used to estimate the number of AF+ only, and the rest of the patients are sent to the inconclusive branch where some of them are true negative (and do not need any repeat testing), and some require repeat testing.

44. The economic submission states that there is a maximum of 2 repeated diagnostic tests, however "HOLTER" worksheet looks as though 3 repeat tests have been included (Column R). Can you explain?

Response: You need to look at column N. The other columns show the results of primary and subsequent monitoring tests. You see three records because for the second round, a % of patients receive Holter 7d and some receive other devices. So it is two rounds of repeat testing but in each round different monitoring devices could be offered by the clinician to the patients.

45. The summary states that cost savings are largely driven by reduction in number of health care visits. The cost of KardiaMobile ECG review has not been included in the technology costs; however the IFU states that KardiaMobile cannot be used for clinical diagnosis without clinical interpretation. Can you explain why this has not been included in the model?

Response: Due to the high negative predicted value of KM, only positive cases need to be checked with a clinician. So, in the base-case analysis we have assumed that only the KM positive tests will be seen by a clinician. We have developed the functionality in the model so that you can assess

alternative scenarios where "all cases" or "positive and inconclusive" results will be seen by a clinician. Please check cell "H9" in the "Results" sheet of the model.

46. Cost of GP visit was based on per patient contact of 9.22 minutes.
    a. No reference for this number is provided. Where did this number come from?

Response: This is based on the standard GP visit duration as reported by PSSRU.

https://www.pssru.ac.uk/pub/uc/uc2020/2-communityhcstaff.pdf

Again, this has been built into the model just in case a small proportion of patients might be seen by a GP as opposed to a cardiologist. In the base-case analysis, we have assumed all patients will be seen by a cardiologist only.

    b. GP visits are not included in base-case (column CI in "KM", "HOLTER" and "Zio" worksheets). Therefore why has it been included in the executable model?

Response: This is a part of model flexibility to run various scenarios if needed. Please see previous response.

47. The model includes QALYs and ICER however these are not normally considered within MTEP processes (which focuses on cost consequence). Can you explain why these have been included?

Response: Due to the rapid AF-detecting capability of KM, it also has an impact on quality-of-life and mortality rate. Therefore, we have developed a dual CCM/CEM. The results of the cost-consequence model are also available in the results sheet of the model.

48. Transition probabilities: probability of true AF positive (KardiaMobile) = 1.00, but probability of true AF positive (KardiaMobile and clinician) = 0.77 – can you explain please?

Response: As per the NICE scope document *(The analysis should explore the impact of using the technology algorithm for trace classification, or interpretation of the ECG trace for detecting atrial fibrillation*), the model runs two scenarios for the intervention:

The results of KM will not be interpretated by a clinician and diagnosis will be only based on KM's algorithm,

The results of KM will be interpretated by a clinician.

Therefore, in the first scenario, all the positive AF cases will be assumed to be true AF (even though we know that some of them are false positive) and will be sent to the AF health state. This is the reason for the differing probabilities depending on whether or not the KM results are interpreted by a clinician.

49. The cost of KardiaMobile is listed as £82.50 – but the breakdown is not stated. Is this an average cost of the single and 6-lead KardiaMobile Heart Monitor? Is the Kardia app free of charge?

Response: We should include price for both devices £124.20 (6 lead) and £82.50 (single lead) which is the hardware cost and only upfront costs required; the app is free. The value in cell "K128" in the "User Inputs" sheet need to be updated please.

50. Technology cost of KardiaMobile is listed as £82.50 per device, but £8.96 per monitoring session is inserted into the model we assume to account for the device being reusable. [This is based on 2 year life of device and 14 days monitoring with KardiaMobile with 5 days

between patients; (2*365)/(14+5) = 38 uses in device lifetime, and a total cost of £344.25]. Device breakage/loss and battery not included. Can you explain?

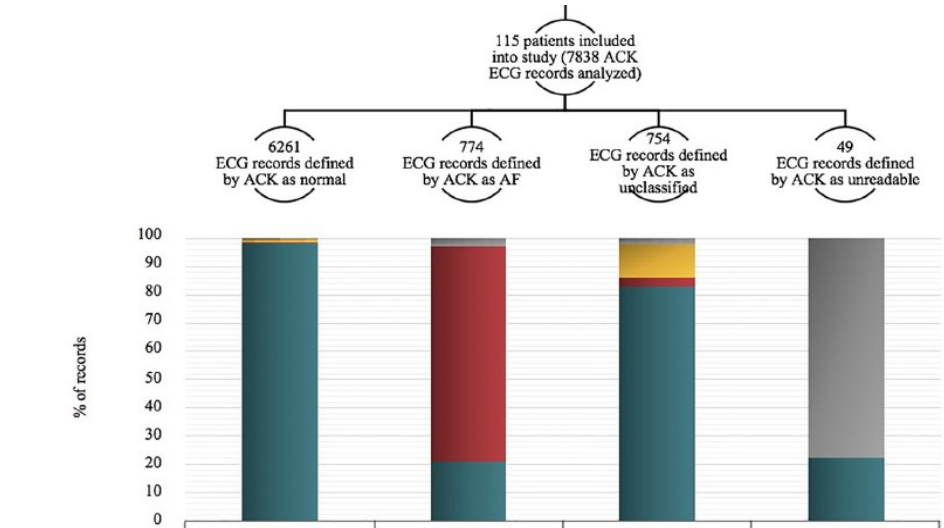
Response: These are all included in the price costs (£82.50 per device).

51. The costs sourced from Zio (MTG52) state "inflated to 2019". However MTG was published in 2020 and consumer price index to inflate 2020 to 2021 is not available from ONS yet. Inflation of 1.0183 appears to have been applied. Can you explain the inflation?

Response: The costs in the Zio submission are based on reference costs in 2017-2018. Therefore, we applied the associated inflation rate to all costs in this document to estimate costs in 2019.

52. The submission states that "initial inconclusive results from the device may also undergo subsequent clinical assessment". Does this mean unclassified readings? Or unreadable readings? Or both combined? From some of the calculations this includes "normal sinus" outcomes – however this seems counterintuitive?

Response: Sorry for the confusion and not presenting this clearly. As per the Hermans et al, 2021 study there are two types of unreadable tests: 1) Based on the KM device algorithm and 2) based on clinical opinion. The number of unreadable results based on the KM device algorithm is very low (less than 1% (0.63%)) the majority of the time and patients can just repeat another 30 seconds, i.e., another 14 days monitoring does not need to be repeated. We have not included this in our analysis. But those tests that were classified either as unclassified or unreadable by the clinicians are all included in inconclusive results.



	SR	AF	unclassified	unreadable
unreadable	0.2%	2.6%	2.8%	77.6%
other arrhythmias	1.2%	0.1%	11.9%	0%
AF	0.1%	76.5%	3.2%	0%
SR	98.5%	20.8%	82.9%	22.4%

53. Clinical parameters (Table 3) states a waiting time for diagnosis with Zio of 3 (2-5) days sourced from Kaura et al. 2019. However this study randomised patients with previous stroke/TIA to either standard care (Holter monitoring, approx. 24 hours) or patch based monitoring (Zio patch, 14 days). Primary outcome was detection of AF lasting at least 30

seconds within 90 days. This study does not report waiting time for diagnosis, therefore it is unclear where the company obtained these values?

Response: The waiting time means the time between finishing monitoring and availability of the results for clinician review. We assumed three days for all procedures considering weekends and workloads in secondary care. But this can be varied in the model using other values. In the MTG52 (page 220) it is mentioned that *"from the patch being received at the company to them being alerted that the report was available (2 days)".*

54. "Inter calculations" worksheet appears to use the per-recording diagnostic accuracy of KardiaMobile and KardiaMobile+clinician interpretation (excluding results "unreadable" on KardiaMobile) and converts into a per-patient proportion. The breakdown per-patient was not reported in Hermans et al. 2021, and the approach taken is not explained explicitly in the spreadsheet, therefore can you explain your calculations and approach?

Response: We have tried to estimate the proportion of patients with different results, i.e., positive (true and false), negative (true and false), and inconclusive using KardiaMobile.

As you mentioned, first we have estimated the redistribution of different outcomes after KardiaMobile + Clinician interpretation.

TABLE A	SR (not AF)	AF	Unclassified
Positive	0.10%	76.50%	3.20%
Negative	99.70%	20.90%	94.80%
Unclassified	0.20%	2.60%	2.00%

In the next step, we have estimated the probability of each outcome after excluding unreadable results from KardiaMobile. Then, we have applied the above redistribution on the estimated new probability of each outcome in order to estimate the probability of each outcome (positive, negative, and inconclusive) in KardiaMobile + Clinician.

TABLE B	Positive results	Negative results	Inconclusive
KardiaMobile	9.94% =774/(7838-49)	80.38% =6261/(7838-49)	9.68% =754/(7838-49)
KardiaMobile + Clinician	7.99%	91.40%	0.61%

Then we have converted the % of each outcome at ECG records level to the proportion of patients, considering that we know the exact number of true positive cases (29) reported by the Hermans et al, 2021 study. In the next step, we estimated how many patients receive positive results using KardiaMobile. To do so, we used the values in column AF in TABLE A. Later we have relatively distributed the rest of the patients between negative and inconclusive using the values in TABLE B.

For example, if we only rely on KardiaMobile test results then 32.96% of all cases (n=115) will be diagnosed as AF, some of which are false positives. We have considered clinician opinion as gold standard and we have assumed there are only 29 real AF among the 115 patients.

TABLE C	Positive results	Negative results	Inconclusive
KardiaMobile	32.96%	59.83%	7.21%
KardiaMobile + Clinician	25.22%	74.28%	0.50%

In the next step, we have calculated the number of patients or probability of different outcomes. For the estimation of repeat monitoring after false positive, we estimated the residual of proportion of false positives detected by the clinician (20.90%) to all non-true positive cases (100%-76.50%).

For the estimation of the probability of repeat monitoring after inconclusive results, we consider that when both device and clinician reported the ECGs as unclassified cases (2%).

TABLE D		Distribution parameters	
	Cases/ Mean	Alpha	Beta
KardiaMobile – positive cases	38	69	8
KardiaMobile + Clinician – positive cases	29	85	1
True positive	76.500%	29.07	8.93
True negative	99.70%	68.793	0.207
Repeat monitoring after FP	0.110638298	4.204255319	33.79574468
Probability of AF positive - inconclusive	3.20%	0.256	7.744
Probability of AF negative - inconclusive	94.80%	7.584	0.416
Probability of repeat monitoring after inconclusive	2.00%	0.16	7.84

55. In MTG52 (Zio), the EAC estimated a mean of 1.465 additional tests were required for the group of patients requiring test repetition. Can you confirm cell D85 in "Inter calculations" worksheet is a typo (i.e. 2.465)? Does this impact cell D76 also?

Response: No, that number is correct. Because all patients received at least one AF monitoring.

To estimate the proportion of patients who need test repetition, we have used a weighted average of one test for the proportion of patients who have AF and have been detected by Zio, and those who don't have AF. Moreover, 1+1.465 tests for those who have AF but are not detected in the initial test (i.e., 1-prevalece-AF+). In the case of Zio, the weighted average of number of monitoring would be 1.21. In the next step, we converted this value, considering two time of repeat monitoring (a quadratic equation). Therefore, we estimated a 17% chance of repeat monitoring in the case of Zio.

56. Following the clinical pathway (Section 3 of Clinical Submission), patients with irregular pulse from manual pulse palpation would undergo 12-lead ECG. 12-lead ECG would capture all cases of persistent AF. Therefore can you provide the basis of the assumption of 30.3% prevalence of AF used in the model?

Response: This is based on the CRYSTAL AF study (Sanna et al, 2014), which is consistent with the MTG52 submission also.

LONG-TERM FOLLOW-UP

At study closure, 277 patients had completed the scheduled 18-month follow-up visit, 177 had completed the 24-month visit, 94 had completed the 30-month visit, and 48 had completed the 36-month visit (total follow-up, 815.5 patient-years). A relatively small number of patients were followed for more than 24 months, but at 36 months of follow-up, the rate of detection of atrial fibrillation was 30.0% in the ICM group (42 patients) versus 3.0% in the control group (5 patients) (hazard ratio, 8.8; 95% CI, 3.5 to 22.2; P<0.001) (Fig. 2C).

Downstream stroke model

[redacted]

[redacted] The model uses an estimate of the true prevalence of AF in this population based upon the CRYSTAL-AF study results (Sanna 2014). The sensitivity of the technologies is assumed equal to their

Table 9 Clinical parameters used in the company's downstream stroke model

Variable	Company value	Source	EAC value	EAC comment
True prevalence of AF in	30%	Sanna (2014) (CRYSTAL AF study)	30%	The EAC considers this appropriate

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Table 9 Clinical parameters used in the company's downstream stroke model

Variable	Company value	Source	EAC value	EAC comment
True prevalence of AF in	30%	Sanna (2014) (CRYSTAL AF study)	30%	The EAC considers this appropriate

57. Cost of NOACs (daily) in the model is listed as £1.91. Can you share the exact reference used? And whether a weighted average was used?
    Response: Please see page 248 of 427: https://www.nice.org.uk/guidance/ta607/documents/committee-papers

Table 49 Medication costs

Drug	Daily dose	Pack size	Pack price	Daily cost	Source
Aspirin	75mg od	28	£0.63	£0.02	BNF (cost of 28 tablets (GSL) [25]
Rivaroxaban	2.5mg bd	56	£50.40	£1.80	BNF[25]
Ticagrelor	60mg bd	56	£54.60	£1.95	BNF[25]

Source: Reproduced from CS Table 74. BNF online, accessed November 2018

We used combination of Rivaroxaban and Ticagrelor and inflated to 2019 price using an inflation rate of 1.02 (2018 to 2019).
https://eppi.ioe.ac.uk/costconversion/default.aspx

58. Cost of stroke (first/subsequent years), major bleed, intracranial haemorrhage, MI are referenced to TA607. Can you please state exactly where in TA607 these costs come from? The reference to TA607 states thst costs were inflated to 2019 prices, however TA607 was published in 2019, therefore can you please share any inflation applied.
    Response: Please see page 83 of 427
    https://www.nice.org.uk/guidance/ta607/documents/committee-papers

    We have used the following source to inflate the costs.
    https://eppi.ioe.ac.uk/costconversion/default.aspx

    Although TA607 was published in 2019, the costs included in the table highlighted above were updated using PSSRU 2018. Therefore, we were required to inflate the costs accordingly.

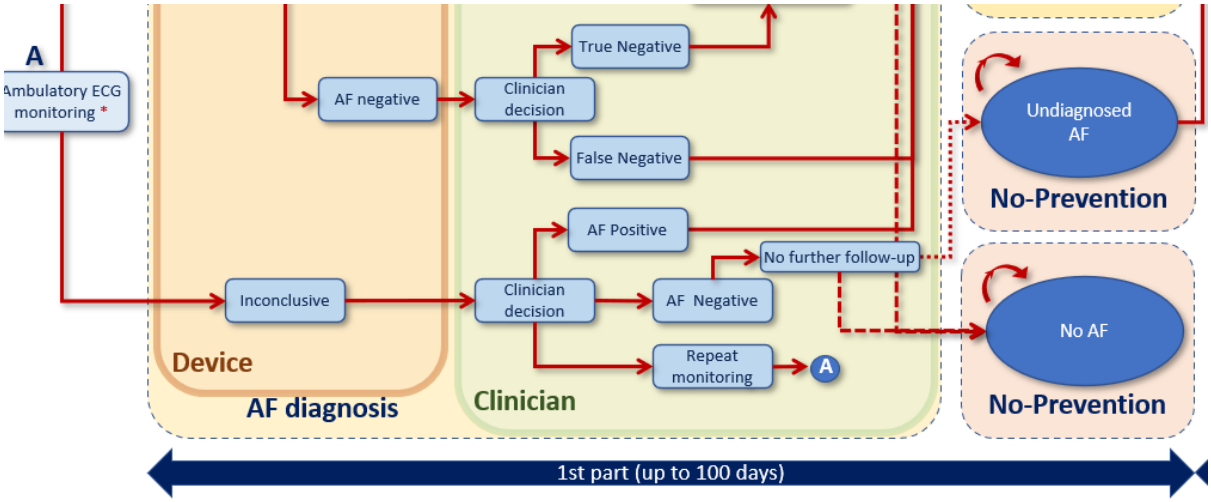
59. Cost of fatal event (£2258) references Walker et al. 2016. Can you please share where you obtained this cost and any inflation applied?

    Response: Please see page 83 of 427
    https://www.nice.org.uk/guidance/ta607/documents/committee-papers

60. At the end of the diagnosis phase the following states are populated:
    a. Can you explain why Zio has fewer diagnosed with AF than Holter?
    Response: The diagnostic yield for Zio is based on the study by Kaura et al, 2019. The Holter arm has higher diagnosis because after the initial test, patients could use CER and therefore this strategy has a higher diagnosis rate.

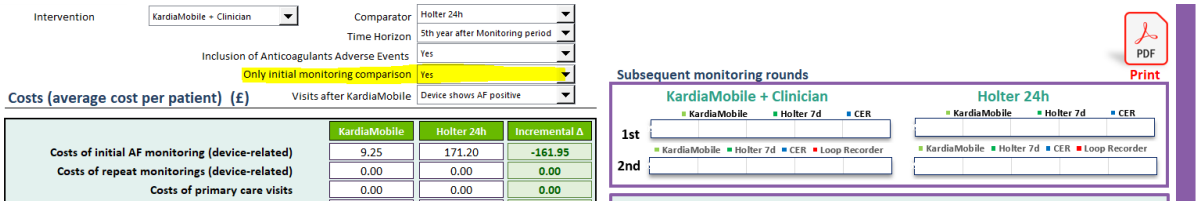
b. Can you also explain why diagnosis of AF starts populating from day 1 in KardiaMobile arm (and not day 4 like the Holter monitor arm? Both have 3 day wait time for diagnosis from the inputs of the model?).
Response: KardiaMobile can detect positive cases and the patient can send the positive results to a clinician straight away after using the KardiaMobile app. The 3 days waiting time in KM is only applied for the non-positive results if they need to contact clinicians (an assumption).

c. Can you also explain who is in the "undiagnosed AF" group – particularly for KardiaMobile which has gone through the app, and been reviewed by a clinician?
Response: Based on the Hermans et al, 2021 study, we believe that undiagnosed AF could be a proportion of patients with AF negative in the conclusive arm, as shown in the figure below. This is due to the high negative predictive value of KardiaMobile. However, in the model, we estimated undiagnosed AF by subtracting detected AF from the prevalence of AF.



	Diagnosed AF	Undiagnosed AF	No AF	Dead
KardiaMobile	25.8% (starts from day 1)	4.5%	69.4%	0.3%
Holter	17.6% (starts from day 4)	12.7%	69.4%	0.3%
Zio	16.6% (starts from day 17)	13.8%	69.4%	0.3%

Response: The above cumulative impact on AF detection is impacted by the switching patterns between various ambulatory ECG monitoring devices during the subsequent monitoring process. If you want to investigate a head-to-head comparison (without considering subsequent monitoring), you can choose the 'Yes' option in the "Only initial monitoring comparison" Combo box in the "Results" sheet of the model (Cell H8).



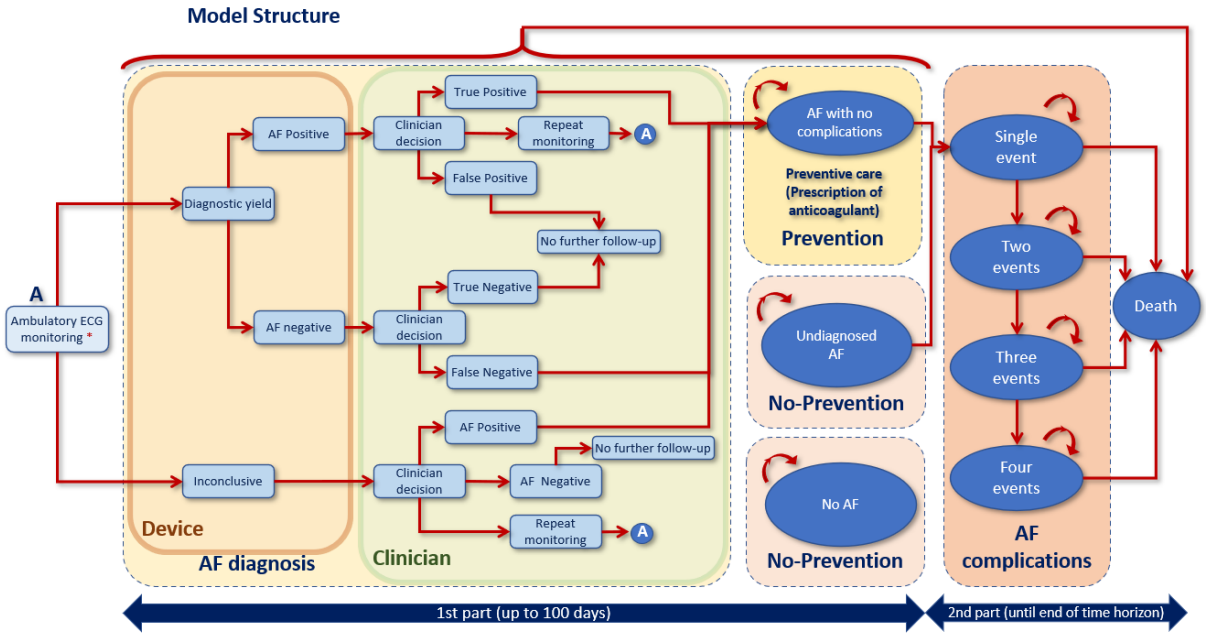
Appendix 8

Additional economic model questions for company (11/05/2021)

Previous questions not answered/additional clarification needed:

1) The model assumptions listed in the Economic Submission states: "In the model, negative and confirmed positive results by the clinician will not lead to repeat ambulatory ECG". However the Model structure in Appendix B confirms that a proportion (0.86% as stated in written response from company received on 11/05/2021), have KardiaMobile then clinical interpretation and then repeated monitoring – which contradicts this. Can you explain?

Response: Thank you for the comment. You are right. We updated the model structure diagram. The model works considering the above assumption:



2) *Where* did wait time and its distribution 3 (2-5) days come from – it is not from Kaura et al. 2019 as stated in Economic Submission, and is not from MTG52 (which was included in written response from company received on 11/05/2021 which was 2 days for the report from Zio to be available)?

Response: This was based on the MTG52 (page 220/744) (i.e., 2 days' time from return of the device to availability of results) plus one additional day to book an appointment for the patient.

Clinician confidence/acceptance

Contributors were aware that IT software was supporting cardiac technicians to analyse the recordings. This process did not pose any concerns to contributors. All contributors are positive about the technology. They said it worked well with a quick turnaround time from the patch being received at the company to them being alerted that the report was available (2 days). Reports were of a high quality.

Two contributors highlighted that it does not offer 'live feedback' which means there would be a delay in action and treatment if an arrhythmia had occurred during the monitoring period. Implantable cardiac monitors can send an alert on the same day as an arrhythmia has occurred.

Contributors said that potentially cardiac technicians could feel apprehensive about adopting the Zio XT Service because interpretation of results is part of their role.

Model structure/assumption queries:

3) Can you please send an electronic version of the Model Structure (Appendix B in Economic Submission is missing arrows which appear in your previous written responses on 11/05/2021)?

Response: The current model structure used for base-case analysis is the same as the above picture in question 1.

4) Changing rate of repeat monitoring (Holter, CER, Zio: "USER INPUTS" cells I27-29) to 0 does not change the cost of repeat monitoring ("RESULTS") in the Zio arm. Can you please explain?

Response: As the calculated variables, cells (I28 and I29) are provided for display to the users. If you want to cancel out the repeat monitoring rates, you can do that in the "inter calculation sheet" and change values in cells D84, and D93 to zero.

For Holter you can make this change in the user column in the "User inputs" sheet.

5) For the KardiaMobile arm, you can change the Visits after KardiaMobile from "Device shows AF positive" (base-case) to "Device shows AF positive or inconclusive", or "In any case".
   1) The base-case for the comparator arms is "In any case". Can you describe which cell of the model can be altered to enable the comparator arm to be "Device shows AF positive" only?

Response: We did not anticipate this option in the model. If necessary, we would be more than happy to include it in the model quickly. However, as per MTG52 all patients, regardless of the outcome, will need to be seen by a clinician in all comparator arms.

6) The annual risk of intracranial haemorrhage_aspirin ("USER INPUTS" cell I38) and annual risk of bleed_aspirin ("USER INPUTS" cell I42) are 0.55% (ICH_ASA) and 1.15% (MB_ASA) respectively, referencing the Diamantopouls et al. 2016 paper. However in that paper these annual risks refer to an "AF free" population. Can you explain how you used these values?

Response: These are drug-related adverse events (Aspirin) and not related to AF.

7) "HR experiencing major bleeding_Undetected AF patients" 0.510 in "USER INPUTS" worksheet (cell I45). Can you please explain the meaning of this parameter please?

Response: As undetected AF patients will not receive any medication, they are less likely to experience bleeding events than detected AF patients who will receive medication and are at a higher risk of drug-related adverse events.

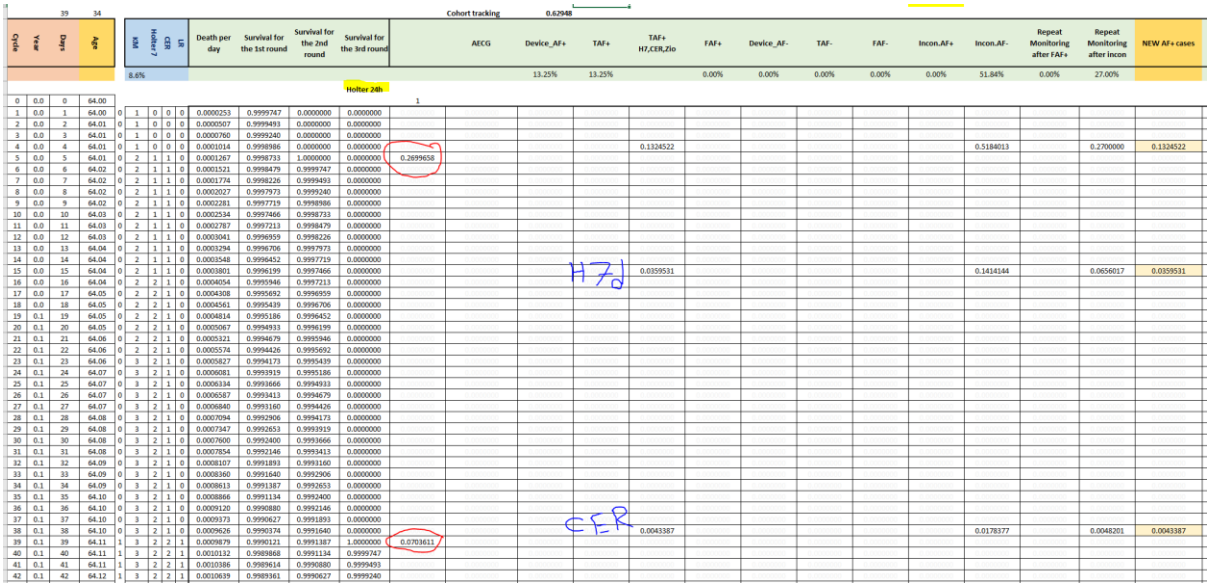
8) An additional day has been added to repeat monitoring. For example, repeat monitoring after initial 24-hour Holter includes 7 day Holter, plus 3 day wait time, but population isn't calculated until 11. Is this a consequence of a tunnel state occupying 1 day time?

Response: In general, yes, we had some difficulties adjusting the time difference between various devices. This is the rationale that we used:

1- Initial monitoring: days required for ambulatory monitoring + waiting time,

2- Second monitoring: initial monitoring + 1 day,

3- Third monitoring: maximum duration of second monitoring + waiting time + 1 day.



As you can see from the above figure, after initial monitoring, Holter 24h, the second monitoring happens on day 5 (one day monitoring time + 3 days assumed waiting time + 1 additional day). The third round of monitoring happens on day 39 (5 days initial monitoring+ max (30+3,7+3) + 1 additional day).

9) Can you confirm that the KardiaMobile arm includes diagnosis and treatment on same day (e.g. "KM" worksheet row 7)?

10) **Response: For KardiaMobile and comparators, patients can receive treatment as soon as the AF positive results have been confirmed. For KardiaMobile, it is very easy to send the results to the doctor using the mobile app, while this is not possible for comparators.**
*"USER INPUT" worksheet rows 51-54 include Hazard rates for prior stroke, major bleeding, MI and ICH for no treatment vs warfarin, NOAC vs warfarin, Aspirin vs warfarin. However the reference provided (Hill et al 2020) compares apixaban to rivaroxaban (and does not mention Aspirin or warfarin). Can you explain where the Hazard Ratios in the model have come from?

Response: Have you checked the supplementary information? In the supplementary information, you can find the below table:

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Hazard of events

	Hazard ratio of experiencing event				
	Stroke	**Major bleed**	**MI**	**ICH**	**ACM**
Base probability	0.012	0.066	0.008	0.009	0.038
Event history adjustment					
Prior stroke	4.015	1.391	1.000	1.632	1.323
Prior major bleed	1.323	3.320	1.000	3.525	1.323
Prior MI	1.246	1.246	1.000	0.942	1.030
Prior ICH	1.786	1.391	1.000	10.176	1.323
No prior MI	1.000	1.000	1.000	1.000	0.972
No prior stroke	1.000	1.000	1.000	1.000	0.758
Regimen adjustment[33]					
Warfarin*	1.000	1.000	1.000	1.000	1.000
DOAC*	0.900	0.820	0.860	0.460	0.890
No treatment*	3.000	0.510	0.510	1.000	1.650

ACM: all-cause mortality; DOAC: direct oral anti-coagulant: ICH: Intracranial hemorrhage: MI: myocardial infarction
*Regimen adjustment relevant to warfarin

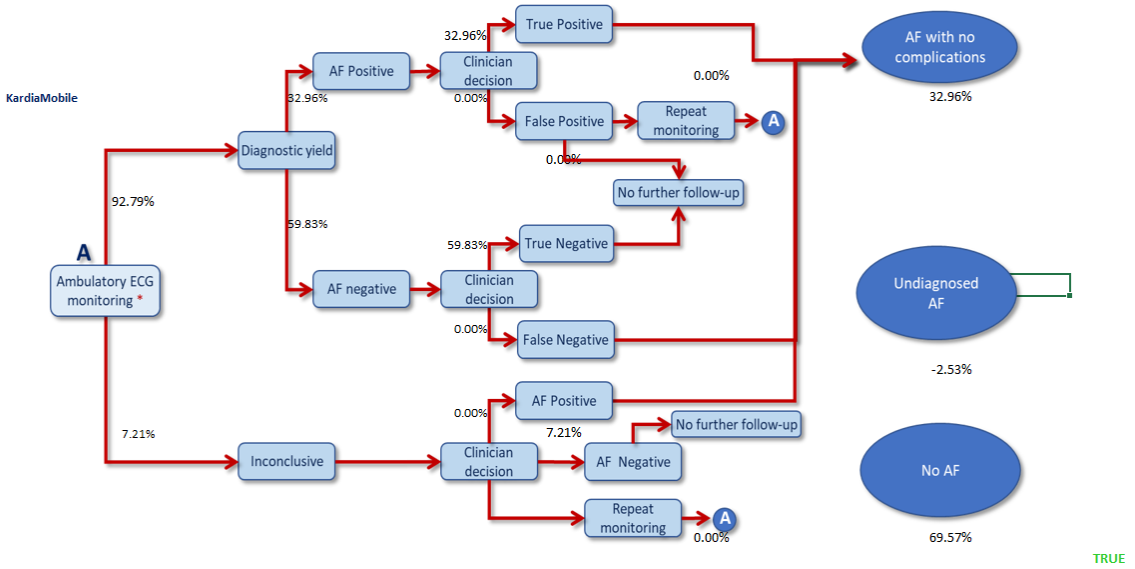
11) ***For Aspirin, as we mentioned in the reference cell, we assumed an equal relative risk of complication based on the results of Diamantopoulos et al. (2016) between Aspirin vs warfarin (1.15%/1.11%).** Can you explain why the probability of true AF negative for KardiaMobile is modelled as 1.00, however the probability of true AF negative for KardiaMobile+Clinician is lower (0.997)?

Response: Sorry, for the confusion here. This is due to the names that we have used in the model structure (branch names). "Probability of true AF negative" means the probability of moving to the true negative branch after having a negative result. So, when we only rely on KardiaMobile, if the result from KardiaMobile is negative then all negative patients will be sent to the true negative branch, but if we rely on KardiaMobile+Clinician some of the negative results are false negatives and the patients will be sent to the 'false negative' branch. Therefore, the probability of true AF negative for KardiaMobile+Clinician is less than 1.

12) Can you explain why the probability of repeat monitoring after inconclusive test (KardiaMobile) is 0.00, but 0.02 when KardiaMobile+Clinician?

Response: We have assumed that repeat monitoring after an inconclusive test could happen only if clinicians are involved in the diagnostic process. When we select the exploratory analysis of

'KardiaMobile alone' and if the results from KM are inconclusive then the device can not suggest repeat monitoring. Therefore, we assumed all inconclusive results are equal to AF negative in the absence of clinician interpretation. Please see the below figure.



It is worth noting that we have developed the functionality in the model to run a scenario where we completely rely on KardiMobile as per the NICE scope document; however, in reality, relying on the device is not a clinically feasible scenario because for AF positive cases the ECG results need to be seen by a clinician before offering any medication.

13) Can you explain why the probability of no AF (KardiaMobile)-inconclusive is 0.0, however 0.5 with KardiaMobile+Clinician?

Response: This parameter was used in one scenario analysis which is not the case in our current base-case analysis. We had assumed that if the results from KM are inconclusive how patients should be distributed between undiagnosed AF and no AF. However, as mentioned, this scenario is not functional in our current submission. We apologize if this causes any confusion.

Parameter queries (discrepancies between Economic Submission and model):

Response: Apologies for the discrepancies between model data and some of the data included in the economic submission. Due to the volume of model parameters and the number of iterations of the model that were developed in the process of finalising the submission, some parameters from old iterations of the model were inadvertently included in the final submission. We can confirm however that the model parameters and results are accurate, and that the outdated parameter values (highlighted below) in the economic submission can be ignored. If it would be helpful and agreeable, we can update the values in the submission form to ensure they are consistent with the model values.

14) Page 39 of company submission states that the probability of repeat monitoring after inconclusive test (Zio) is 0.00. However the model ("USER INPUT" cell W68) states 78.96%. Can you confirm this is an error in the Economic Submission?

Response: Think you are referring to 'probability of AF negative – inconclusive' (78.96%) rather than the probability of repeat monitoring parameter (query 16 below). However, you are correct in pointing out that the economic submission value doesn't match the value included in the model, and we can confirm that the model value is accurate.

15) Page 39 of company submission states that the probability of repeat monitoring after inconclusive test (CER) is 1.00. However the model ("USER INPUT" cell I81) states 78.73%. Can you confirm this is an error in the Economic Submission?

Response: Think you are referring to 'probability of AF negative – inconclusive' (78.73%) rather than the probability of repeat monitoring parameter (query 17 below). However, you are correct in pointing out that the economic submission value doesn't match the value included in the model, and we can confirm that the model value is accurate.

16) Page 39 of Economic Submission states that the probability of repeat monitoring after inconclusive test (Zio) is 0.05. However the model ("USER INPUT" cell W69) states 21.04. Can you confirm this is an error in the Economic Submission?

Response: Can confirm.

17) Page 39 of Economic Submission states that the probability of repeat monitoring after inconclusive test (CER) is 0.00. However the model ("USER INPUT" cell I82) states 21.27. Can you confirm this is an error in the Economic Submission?

Response: Can confirm.

18) Page 40 of Economic Submission states probability of no AF (Zio) – inconclusive is 0.89. However the model ("USER INPUT" cell W70 states undiagnosed AF inconclusive is 13.76, therefore no AF inconclusive would be 1.0-0.1376=0.8624). Can you confirm this is an error in the Economic Submission?

Response: Yes, these values were ultimately not required for the base-case scenario in the model and should have been omitted from the economic submission.

19) Page 40 of Economic Submission states probability of no AF (CER) – inconclusive is 0.89. However the model ("USER INPUT" cell I83 states undiagnosed AD inconclusive is 14.11, therefore no AF inconclusive would be 1.0-0.1411=0.8589). Can you confirm this is an error in the Economic Submission?

Response: Yes, these values were ultimately not required for the base-case scenario in the model and should have been omitted from the economic submission.

20) Page 40 of Economic Submission states:

a. First round of repeat monitoring after Holter (24h) includes 80% Holter (7days) and 10% CER. However model states 90% and 10% respectively. Can you confirm this is an error in the Economic Submission?

Response: Can confirm.

b. First round of repeat monitoring after Holter (48h) includes 90% Holter (7 days) and 10% CER. However model states 80% and 20% respectively. Can you confirm this is an error in the Economic Submission?

Response: Can confirm.

21) Page 42 of Economic Submission states "% of ICH that is haemorrhagic stroke = 0.6). What does this mean? Where is this included in the model (worksheet and cell reference would be helpful)?

Response: This value was ultimately not required for the final version of the model and should have been omitted from the economic submission.

22) Page 42/43 of Economic Submission states hazard ratios of Stroke for no treatment, NOAC and Aspirin against warfarin. However in "USER INPUT" worksheet cells I55-I57 are empty, can you explain?

Response: Yes, these values were ultimately not required for the final version of the model and should have been omitted from the economic submission.

23) Page 43 of Economic Submission states hazard ratios of Major Bleeding for no treatment, NOAC and Aspirin against warfarin. However in "USER INPUT" worksheet cells P55-P57 are empty, can you explain?

Response: Yes, these values were ultimately not required for the final version of the model and should have been omitted from the economic submission.

24) Page 43 of Economic Submission states hazard ratios of ICH for no treatment, NOAC and Aspirin against warfarin. However in "USER INPUT" worksheet cells AD55-AD57 are empty, can you explain?

Response: Yes, these values were ultimately not required for the final version of the model and should have been omitted from the economic submission.

25) Page 43 of the Economic Submission states that the hazard ratio of MI when on no treatment compared to warfarin was 0.51 (however "USER INPUT" worksheet cell W55 states 0.860). Can you confirm this is an error in the Economic Submission?

Response: Can confirm that the value in the economic submission is incorrect.

26) Page 43 of the Economic Submission states that the hazard ratio of MI when on NOAC compared to warfarin was 0.86 (however "USER INPUT" worksheet cell W56 states 0.510). Can you confirm this is an error in the Economic Submission?

Response: Can confirm.

2) Page 43 of the Economic Submission states that the hazard ratio of Death when on aspirin compared to warfarin was 1.04 (however "USER INPUT" worksheet cell AK57 states 1.000). Can you confirm this is an error in the Economic Submission?

Response: Can confirm. Yes, parameter value of 1 in the model is correct.

Appendix 9

Questions to Experts 20210512 - Collated responses

Expert #1	David Ferguson Arrhythmia Advanced Nurse Practitioner University Hospitals Morecambe Bay
Expert#2	Dr Ruth Chambers Ex- Staffordshire clinical lead for technology enabled care services programme, digital workstream & Honorary professor Keele University, Visiting Professor Staffordshire University
Expert#3	Matt Reed, Consultant, NRS Clinician and RCEM Professor of Emergency Medicine, NHS Lothian
Expert#4	Kevin McGibbon Arrhythmia Clinical Nurse Specialist University Hospital of North Midlands

Expert#5		Shona Holding Cardiovascular Specialist Nurse Practitioner
General Comments		
Expert#1		I must stress this is what we do in our trust but other trusts use kardiaalivecor in different ways
Expert#2		My response as retired GP, who's overseen some technology enabled care projects in last 3 years or so including screening with AliveCor & trial of 2 types of up to 14 day holters in 5 practices in Staffordshire
Expert#3		No additional comments
Expert#4		No additional comments
Expert#5		I have attempted to answer most of the questions. If evidence is needed , let me know and I can look the references up
1	The clinical evidence surrounds 5 main subgroups:	Expert #1: • I would add patients with paroxysmal atrial flutter or atrial tachycardia, we also use it for patients with symptomatic ectopy to confirm diagnosis

	• patients with undiagnosed palpitations (negative 12-lead ECG) • patients with history of AF, who have received treatment (ablation, cardioversion, or medical therapy) to restore sinus rhythm and used KardiaMobile to identify recurrence • patients with diagnosed AF to assess AF burden • patients with transient AF after surgery or hospitalization who reverted back to sinus rhythm prior to discharge, and used KardiaMobile to identify recurrence • patients after stroke or TIA who were monitored using KardiaMobile The company has included an AF prevalence of 30% in their economic model. The clinical pathway states that	To my mind patients with undiagnosed palpitations benefit most as KardiaMobile when analysed correctly can diagnose Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, SVT, Ventricular Ectopics and Supraventricular Ectopics Expert #2: • patients with undiagnosed palpitations (negative 12-lead ECG) - **circa 6% identified as needing 12 lead ECG if >65 year olds screened we found** • patients after stroke or TIA who were monitored using KardiaMobile **- circa 30% identified as needing 12 lead ECG if these groups screened I'd guess** Subgroup most likely to benefit - As a primary care expert, it's first group done at scale eg whilst vaccinating with 'flu or COVID jabs in >60 year olds Expert#3: No response Expert#4: Depends on how you weigh benefit but very important to identify AF after stroke/TIA to anticoagulate and protect from further stroke as high risk. Expert#5: [subgroup] 1[patients with undiagnosed palpitations (negative 12-lead ECG)]

	patients would undergo manual pulse palpation, then 12-lead ECG (this would capture all persistent AF). Therefore is the prevalence of 30% used by the company likely in any of the above subgroups? Of the above 5 patient subgroups which is the biggest (i.e. which contains the most patients who may benefit from KardiaMobile)?	
2	What are the criteria that would require a patient to have an implantable cardiac monitoring device?	Expert #1: For episodes of suspected cardiac syncope or suspected atrial fibrillation not diagnosed by any other device.
		Expert#2: Don't know
		Expert#3: Normally undiagnosed syncope thought to be cardiac not detected using non-invasive monitoring in a patient whose syncope frequency is greater than 2 weeks. Implantable cardiac monitoring not really used in AF diagnosis/screening

		Expert#4: Patients in high risk groups for stroke with a low frequency of symptoms. 2-3 x per year
		Expert#5: Intermittent Syncope/LoC , infrequent palpitations(months apart)
3	The economic model submitted by the company includes up to 3 diagnostic tests per patient (1 initial diagnostic e.g. Holter, followed by 2 repeats). Is this likely in clinical practice in any/all of the above 5 subgroups?	Expert #1: Very unlikely in any scenario, we are moving away from holter monitors unless we can have a high probability that patients will have symptoms when the monitor is in place.
		Expert#2: Don't know – the holter patches I've led on trialling in 5 practices up to 14 days continuously had a 45% or so diagnostic rate of AF/significant arrhythmia – depending on patient selection criteria
		Expert#3: We only require 1 diagnostic test per patient
		Expert#4: No response
		Expert#5: Potentially all 5 sub groups
4		Expert#1: 24 hr most commonly used to identify rate and rhythm

	Can you advise which duration of Holter monitor is most commonly used in NHS practice: 24 hour, 48 hour or 7 days?	Expert#2: At present usually up to 48 hours in CCGs I know of; though our trial of up to 14 days showed economically justified by it often being days 3-5 that recorded heart tracings indicated the arrhythmia diagnoses
		Expert#3: Practice very variable across the UK, 24 hour most common in our practice
		Expert#4: 24 hour tape most common in local monitoring
		Expert#5: Anecdotally, all commonly used but probably 24 hour most common
5	What duration of continuous event monitoring is most commonly used in NHS practice? Does 30 days sound reasonable?	Expert#1: We only have 7 days as a maximum
		Expert#2: 14 days seems reasonable to me- quite a few patients didn't tolerate >7 days in our 5 practice trial
		Expert#3: ? I think if an event hasn't been captured on Holter, the next continuous monitor most centres would go for is the implantable loop recorder – I am not sure a 30 day continuous monitor is very commonly used (at least I am not aware of its use locally).
		Expert#4: 30 days would be the common maximum.

		Expert#5: Not sure?
6	The company has included costs for 10 minutes nurse time (hospital based band 6 nurse) per patient in order to assist with setting up the Kardia app and training the patient on KardiaMobile use. Is this reasonable?	Expert#1: Yes, we allow 20 minute appointments depending on the patient, some need more time. We use band 5 physiologists for this
		Expert#2: Yes- with online 'handbook' available too with link to video for subsequent reminder of nurse advice/guidance.
		Expert#3: I think this is reasonable based on our clinic experience, probably slightly longer (15-20 mins) if the patient hasn't yet downloaded and installed the Kardia app beforehand.
		Expert#4: Yes
		Expert#5: 20-30 min with a HCA , ask pt to down load app beforehand will save time.
7	Time to review ECGs is not included in the company economic model for any device.	Expert#1: It varies so much it's difficult to answer. Our clinical physiologists (band 5) review the kardiaalivecor rhythm strips and anything abnormal or suspicious is sent to the arrhythmia nurses (band 7)

	• Is it valid to assume that ECG review time across all of the below devices is comparable?
	  ○ 24-hour Holter monitor results
	  ○ 48-hour Holter monitor results
	  ○ 7 day Holter monitor results
	  ○ 14 day Zio patch results
	  ○ 30 day CER results
	  ○ 14-days of 30 second KardiaMobile ECGs
	• If not, what approximate time would be required to review each
	• Who would review the ECG (cardiologist, electrophysiologist etc)?
		Expert#2: I'm not sure what your question is asking- with our 5 practice trial of up to 14 day holters in 5 practices the irthythm and cardiologic companies provided electrophysiologist reviews & reports; we got independent cardiologist to review circa 80 patients' reports & he added extras arund one if 15 reports & did not disagree with any.
		
		Expert#3: KardiaMobile ECGs likely to be reviewed by clinician i.e. cardiologist, general medic
		
		First 3 and 30 day CER would be reviewed by NHS local electrophysiologist
		
		Zio would be reviewed by iRhythm based electrophysiologist
		
		Expert#4:
		
		If not, what approximate time would be required to review each
		
		Would be fairly similar
		
		Who would review the ECG (cardiologist, electrophysiologist etc)?
		
		Commonly a technician summary then a specialist nurse or GP /cardiologist review.
		
		Expert#5:
		
		Is it valid to assume that ECG review time across all of the below devices is comparable? **No**

		If not, what approximate time would be required to review each o 24-hour Holter monitor results **10 mins** o 48-hour Holter monitor results ? **approx. 30 mins** o 7 day Holter monitor results ? **approx. 1hours** o 14 day Zio patch results ? **not used this before** o 30 day CER results ? **not used this before** o 14-days of 30 second KardiaMobile ECGs **approx 30 mins** Who would review the ECG (cardiologist, electrophysiologist etc)? **cardiac physiologist, arrhythmia nurse or nurse with ECG skills GPwSI cardiology**
8	1. If you have previously issued KardiaMobile to patients: o what was the prescribed/recommended duration of patient use (e.g. 7 days, 14 days, 1 month, 3 months)?	Expert#1: • prescribed/recommended duration of patient use - **2 months** • what frequency do you tell patients to use? - **Only when symptomatic with palpitations** • do you inform patients to email the ECG recording directly to the hospital for review? - **yes**

	○ what frequency do you tell patients to use? Is this only when symptomatic? ○ do you inform patients to email the ECG recording directly to the hospital for review? ○ do you inform patients to email all ECG recordings? Or only “Possible AF”? Or only “Possible AF” and “Unclassified” results? All symptomatic recordings, or stroke team would use them in a different way and may ask the patient to send in 4 per day ○ How soon are KardiaMobile ECGs reviewed by a clinician (counting from when sent)?	• do you inform patients to email all ECG recordings? Or only “Possible AF”? Or only “Possible AF” and “Unclassified” results? - **All symptomatic recordings, or stroke team would use them in a different way and may ask the patient to send in 4 per day** • How soon are KardiaMobile ECGs reviewed by a clinician - **Mon/Wed/Fri**
		Expert#2: Haven’t done so
		Expert#3: • prescribed/recommended duration of patient use - **We have given it out for periods between 14 and 90 days – I would suggest 1 months would be optimum with a mechanism of recalling a patient early if a significant rhythm has been recorded (i.e. patient triggered recall or Kardia dashboard**) • what frequency do you tell patients to use? - **Depends on the indication – for asymptomatic AF screening/AF load, daily recordings should be best – for palpitation indication then only when symptomatic** • do you inform patients to email the ECG recording directly to the hospital for review? **No – we arrange a follow up appointment to review all tracings, AF is not immediately life threatening**

		• do you inform patients to email all ECG recordings? Or only “Possible AF”? Or only “Possible AF” and “Unclassified” results? - **No – we arrange a follow up appointment to review all tracings, no rhythms are immediately life threatening** How soon are KardiaMobile ECGs reviewed by a clinician - **On return of the patient to clinic (14-90 days)**
		Expert#4: • prescribed/recommended duration of patient use - **Often until a result is obtained, so from short to long term**. • what frequency do you tell patients to use? - **Would vary depend on the group.** • do you inform patients to email the ECG recording directly to the hospital for review? - **Email, or report verbally on phone clinic or show on video clinic** • do you inform patients to email all ECG recordings? Or only “Possible AF”? Or only “Possible AF” and “Unclassified” results? - **Usually all or most**. • How soon are KardiaMobile ECGs reviewed by a clinician - **Variable**.
		Expert#5: o what was the prescribed/recommended duration of patient use (e.g. 7 days, 14 days, 1 month, 3 months)? **1month or until dysrhythmia captured (eg could be after 2 days)**

		o what frequency do you tell patients to use? Is this only when symptomatic? **Yes.** o do you inform patients to email the ECG recording directly to the hospital for review? **Yes emailed to a secure dedicated email address** o do you inform patients to email all ECG recordings? Or only "Possible AF"? Or only "Possible AF" and "Unclassified" results? **All recorded during symptoms** o How soon are KardiaMobile ECGs reviewed by a clinician (counting from when sent)? **Within 1 working day**
9	If patients were diagnosed with AF is the following medication prescribing appropriate - 5% no medication - 5% aspirin - 10% warfarin - 80% NOAC	Expert#1: Impossible to say but warfarin is less than 10% and we don't use Aspirin for AF
		Expert#2: - 5% no medication - depends on CHADSVasc scores - 80% NOAC - usual
		Expert#3: Depends on local practice but likely to along these lines
		Expert#4: - That would be a reasonable approximation

		Expert#5: - aspirin should never be prescribed if target pop is >65, then 80% NOAC, 10% warfarin , 5-10% no medication may be more realistic I think
10	If patients were diagnosed with AF, and received medication is the following rate of major bleed appropriate: - 1.15% Aspirin - 1.11% warfarin - 13.40% NOAC	Expert#1: NOAC is far less than 13.4% but you would need to look at recent studies for accurate figures
		Expert#2: don't know
		Expert#3: No response
		Expert#4: - This is wrong. Similar risk in all groups <5%. More like aspirin 1% DOAC 3% Warfarin 4% https://www.sparctool.com/
		Expert#5: Difficult to put a % on this bleed risk between aspirin and warfarin was found to be negligiable All NOACs are associated with a similar or lower ICH bleed risk compared to warfarin. I can find evidence to back this up if required.
11	If patients were diagnosed with AF, what NOACs would be prescribed (are	Expert#1: Ticagrelor is not a NOAC, we would use Rivaroxaban, Edoxaban, Apixaban or Dabigatran

	Rivaroxaban and Ticagrelor appropriate)?	Expert#2: I'm a retired GP (3 years) and thus don't know what practising GPs now doing.
		Expert#3: We use Apixaban, Ticagrelor is not a NOAC
		Expert#4: The 4 available DOACS are apixaban/eliquis dabigatran/pradaxa edoxaban/lixiana rivaroxaban/xarelto Ticagrelor is not anticoagulation but antiplatelet so more in the aspirin, clopidogrel family
		Expert#5: Choosing a NOAC is guided by bleed risk, stroke risk, renal function as well as compliance NOACs and ticagrelor are not recommended due to high bleed risk compared to concomitant use with aspirin or clopidogrel ..
12	What is the time lapse between confirming AF diagnosis and the start of treatment in your clinical practice? Also are there any additional staff costs in relation to reviewing patients' ECG	Expert#1: once diagnosis is confirmed I have a kardiaalivecor clinic on a Friday morning so would ring the patient from there and suggest treatment options to the patient. I would then write to the GP and suggest they start medication if that was appropriate. Currently there are no additional staff costs in looking at the kardiaalivecor traces as we are trying to reduce the amount of ambulatory monitoring we do so clinical investigations

		staff involved in analysing those have been moved to analysing kardiaalivecor traces. Where we are struggling is with arrhythmia nurse time to speak to patients and GP's once diagnosis has been made and I am making the case for another part time arrhythmia nurse to cover remote monitoring, not just kardiaalivecor but other single lead monitors and loop recorders as well.
		Expert#2: Bear in mind I've not been in clinical practice (except vaccinating!) for 3 years. In the 5 practices trialling the 14 day holters, all practices took responsibility for starting patients on anticoagulants if justified when proven to have AF by holter analyses and with associated CHADSVasc score within one week. For the 130 or so practices to whom we've given AliveCors after they attended a best practice workshop, my impression is from individual informal feedback similar responses- arrange 12 lead ECG after AliveCor screening indicated probable AF in surgery/on home visit - might take (pre-pandemic) 1-2 weeks/not every practice has 12 lead ECG and some referred to community service commissioned by CCG; then show a GP the ECG; then book in for consideration of anticoagulant eg 1-2 weeks normal. So staff costs would be the time for these investigations/GP review eg 10 mins consultation.
		Expert#3: We confirm and commence treatment at the same visit. Reviewing the patients ECGs takes around 5 minutes of staff timer and this is built into our clinic time slots.

		Expert#4: If I am notified of a patient with AF who is not anticoagulated, I tend to ring them very quickly for an ad hoc phone clinic. If I cant get hold of them they are written to with an urgent appointment. Usually very little delay between diagnosis and treatment unless there is a good reason eg complicated anticoagulation issue or patient declines initially or bleeding risks to be modified. On average most get immediate anticoagulation and a few days wait for small group. No additional costs for ECG review. Thanks.
		Expert#5: Time lapse from diagnosis to treatment varies but can be day of diagnosis if all available bloods are up to date but would aim to treat within 1-2 weeks , All our ECGs are stored on ecg cloud and interpreters are in-house cardiology HCPs so no additional cost for us but I believe technomed (cloud) provide an interpreting service for a charge Hope this helps

Appendix 10

GID-MT554 KardiaMobile
Meeting with Company (Economic Model)
13 May 2021 @ 12:00

In attendance:

Newcastle EAC: Andrew Sims (AJS), Kim Keltie (KK), Rachel O'Leary (RO), Emma Belilios (EB)

Company: Sean Warren (SW), Stefan Holzer (SH), Amir Ansaripour (AA), Medhi Javanbakht (MJ)

NICE: Ying-Ying Wang (YYW)

1) **Patient physician data flow walk through and demo (SW, SH)**

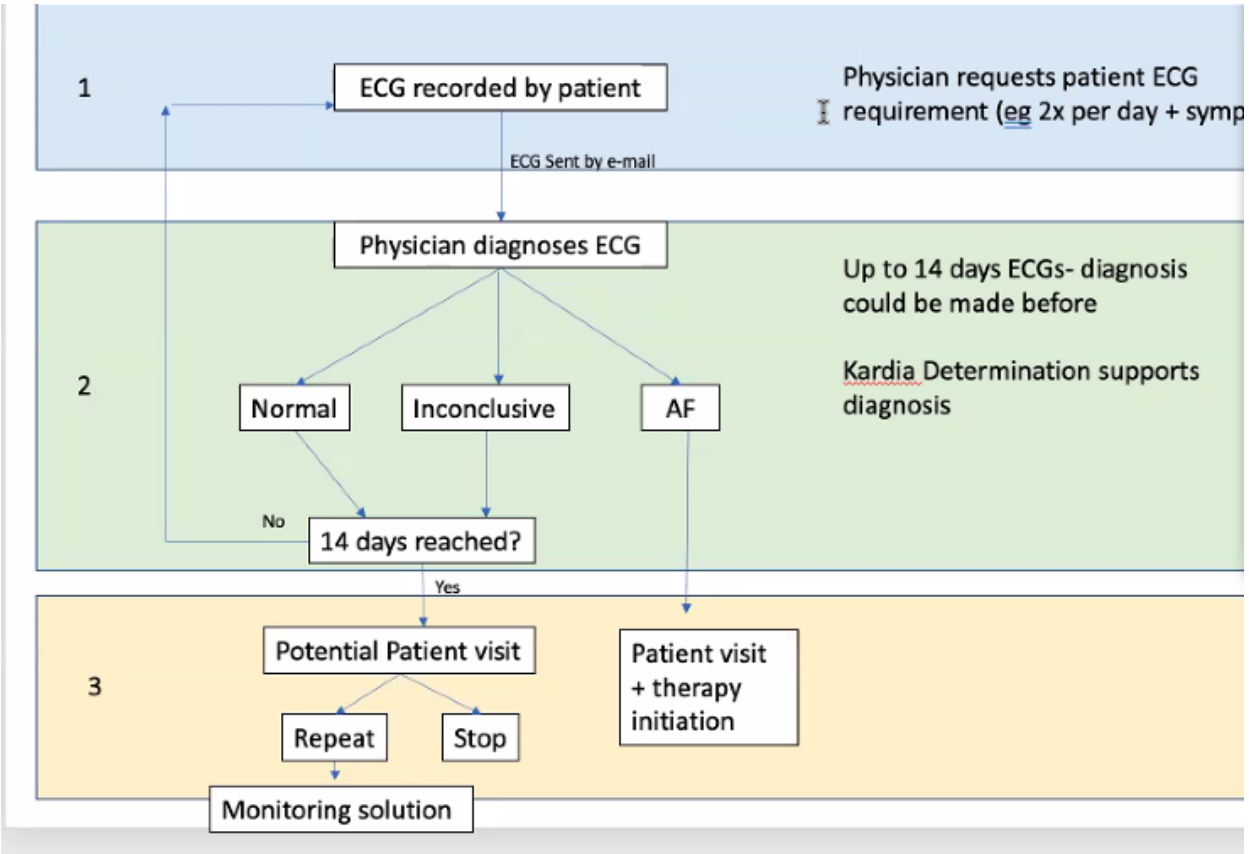
Patient perspective

- Set up account
- Uses device at frequency instructed by physician (usual is twice daily and when symptomatic)
- Open Kardia app to record ECG (30 seconds)
- Result displayed
- Forward pdf to clinician via email

Clinician

- Receives the email
- Opens pdf to determine which patient (ECG trace has name, DOB and timestamp in top corner – information gained from Kardia app during set up; ECG trace also contains Kardia app determination).
- Checks Kardia determination (may check trace)
- If event is detected, clinician would contact patient in. If normal, would continue to monitor for 2 week period, then agree what to do next.

Flow Chart (SW has also provided by email)



Patients would typically be asked to take 2 ECGs per day at set times (to look for 'silent' AF) and additional ECG any time they are symptomatic. The Hermans paper assumes 3 ECGs per day.

YYW asked if the data flow was different for the premium packages, and if patients would be offered the chance to upgrade to the premium package routinely as part of the data flow?

Response: The premium packages give more detailed determination of arrhythmia. This doesn't make a difference for the model as the assessment is only looking at AF which is included in both packages. Model and flow chart are based on the basic package. Premium features are not part of the assessment. The company confirmed only the basic package was included in this evaluation.

AJS asked how would physician contact the patient if they received a pdf showing an abnormality?

Response: SW - clinician would have contact details for the patient from their medical records. Assume contact would be by phone, but it will depend on the organisation's process who makes the call.

AJS - how would the medical practice tie up the emailed recording with the patient record? Whether a dedicated person would receive and review individual patients' email?

Response: SW - ECG would come through either directly to the clinician, or, to a designated mailbox manned by cardiologists (Royal Brompton take this approach). The trace will come through as a pdf, which when opened shows the patient's name and date of birth so it can be assigned to the correct patient. The cardiac team would have a list of patients they are monitoring. There would typically be 10 to 20 devices per organisation, so a manageable amount.

Patient details that appear on the trace are entered by the patient when they register. Matching trace to patient would be done manually. No integration direct to patient record.

2) Model Overview (MJ, AA)

Since the Company Engagement call MJ & AA have made some tweaks to the model (V3.0 shared in advance of the meeting).

Changes in the "inter calculation" sheet.

a. We removed unnecessary data
b. Provide labels for various calculations
c. We realized a miscalculation in cell C47 and corrected it.
d. We provide some adjustments in this sheet to let users run the model with different AF prevalences (as a proxy of different patient populations)

Changes in the "method" sheet

a. The model structure diagram is updated

There are user-modifiable cells on the user input page. Also you need to go to the "RESULTS" worksheet to select:

- the comparator,
- whether repeat monitoring is applied,
- whether to include anticoagulant adverse events, +
- whether the intervention is KardiaMobile only or KardiaMobile+Clinician interpretation, and
- Whether a hospital visit is added to the KardiaMobile arm for patients with a positive determination from the Kardia app, with a positive or unclassified, all patients.

MJ and AA looked at HES data to try to understand the pattern of repeat monitoring, but this could not be determined from the OPCS codes due to lack of granularity. MJ and AA have instead made model flexible enough, so that users can specify devices for repeat monitoring based on expert opinion.

Time for review of ECG can be added to the nurse time ("USER INPUTS" worksheet,cell I70 - it is assumed trained nurse will check the results. Additional visits to discuss results will be with a cardiologist. These assumptions can only be changed for KardiaMobile arm in the model ("RESULTS" worksheet).

EAC not able to replicate the base case scenario - MJ can do this live. Price of KardiaMobile has changed (additional change not listed in above by company).

3) Specific queries on the model

KK - can you go through changes to the model in V3.0?

Response: MJ - Have emailed a full list of changes. Described above.

KK - what is cell A36 (the cell shows "0" and looked like a switch, however this was not labelled)?

Response: Switch for prevalence rate testing. Previously did not allow for dramatic change of AF prevalence but can now switch from assumed rate of 30% to fully flexible user - determined prevalence rate. KK – the ability to change AF prevalence seems odd given that inter-calculations describe diagnostic accuracy of a single study (Hermans et al), with a static pre-test AF prevalence (therefore questions the ability to change the AF prevalence).

MJ and AA are working through responses to the additional list of questions. These will be provided in writing.

Model is driven by a time dependent decision tree. For each period of monitoring, as soon as clinician confirms AF positive case, it is assumed that treatment is started straight away. The Company perceive the key benefit of KardiaMobile is reduced time to diagnosis and therefore treatment.

KK - at the start of the model it is stated that there is a 3 day wait time for diagnosis, so for KardiaMobile it is not clear why there is population of diagnosis and treatment states on day 1 ("KM" worksheet, row 7)?

Response: Have assumed that if KardiaMobile outputs "Possible AF", that confirmed diagnosis and treatment will start the same day. KK stated that this was not described in the Economic Submission.

KK – given the model structure was chosen due to time dependency, why there is a day delay in repeat monitoring. KK shared screen to show example of Holter monitoring: 7 days of Holter, plus 3 day wait time, but state population doesn't occur until day 11. AA - If trace is clear, assumes 4 day wait (2 days assumed from MTG52, plus 1 day to make appointment, plus an additional day for repeat monitoring). KK stated that this was not described in the Economic Submission.

AA - if EAC need a specific scenario modelling, they would be happy to do this.

The submission refers to Company clinical experts, but only one expert (Dr Yassir Javaid) was referenced. Did anyone else provide clinical input to the model parameters?

Response: Dr David Albert, AliveCor chief medical officer. SW will provide details.

4) **Conclusions and next steps**
   - Draft report goes to NICE 14/05/2021, then 2 weeks left of economic assessment
   - Final report goes to NICE 27/05/2021, then to the Company (same day) for fact check
   - Company has until 02/06/2021 to submit fact check comments.
   - EAC has till 04/06/2021.

5) **Communication:**
   - All emails go to Kim, Ying-Ying, Lizzy, Victoria, Emma (covers all bases).

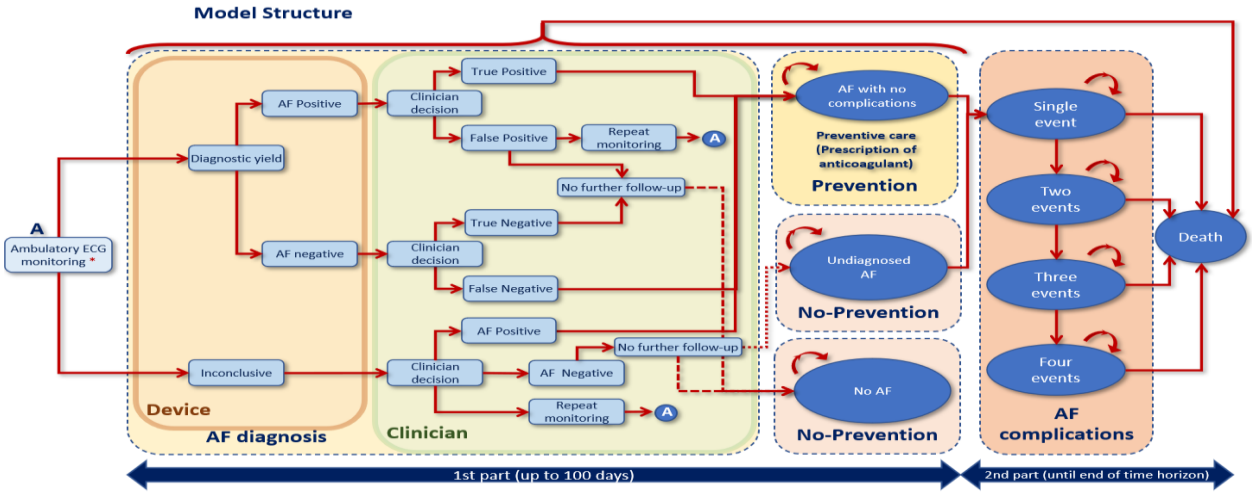
Appendix 11

List of all changes in KardiaMobile economic model V3.0:

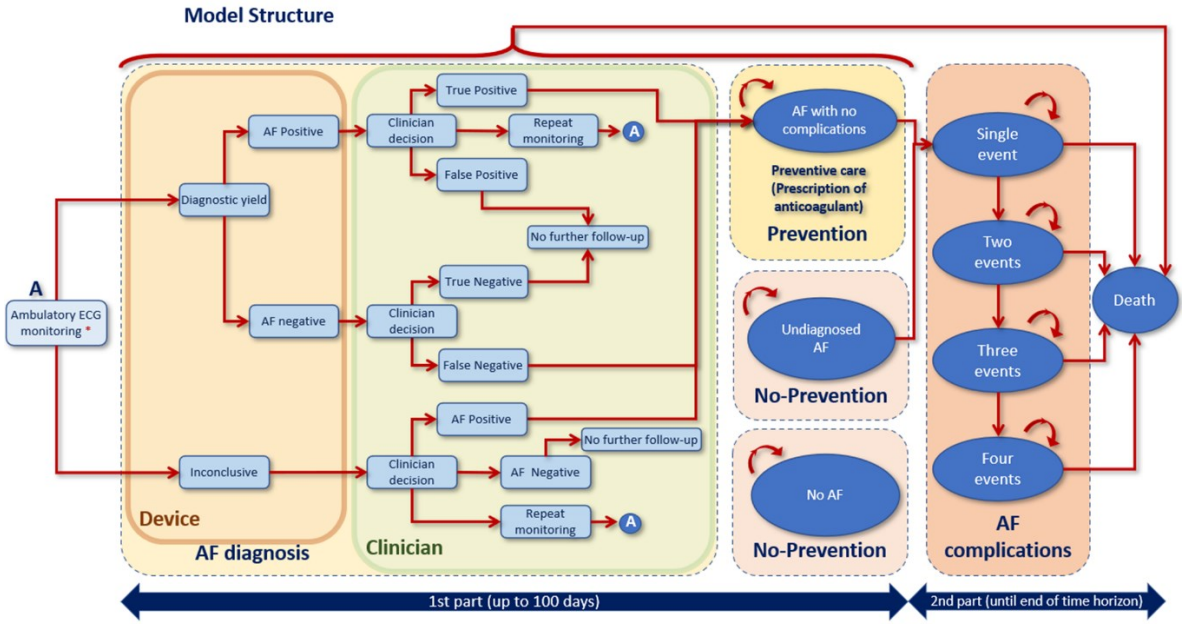
1- Method Sheet:

The model structure has been updated

Version 2.1:



Version 3.0:



2- “Inter calculation” Sheet

A: Intermediate calculations for KardiaMobile:

A1: We added labels for tables, as can be seen below:

Version 2.1:

	SR	AF	Unclassified	
Positive	0.10%	76.50%	3.20%	
Negative	99.70%	20.90%	94.80%	
Unclassified	0.20%	2.60%	2.00%	
N	115			
N+ (KardiaMobile)	29			
	Positive results	Negative results	Inconclusive	
KardiaMobile	0.099370908	0.803825908	0.09680318	TRUE
KardiaMobile + Clinician	0.079920272	0.913952369	0.00612736	TRUE
KardiaMobile	32.96%	59.83%	7.21%	TRUE
KardiaMobile + Clinician	25.22%	74.28%	0.50%	TRUE
KardiaMobile	38	69	8	
KardiaMobile + Clinician	29	85	1	
True positive	76.500%	29.07	8.93	
True negative	99.70%	68.793	0.207	
Repeat monitoring after FP	0.110638298	4.204255319	33.7957447	
Probability of AF positive - inconclusive	3.20%	0.256	7.744	
Probability of AF negative - inconclusive	94.80%	7.584	0.416	
Probability of repeat monitoring after inconclusive	2.00%	0.16	7.84	

Version 3.0:

KardiaMobile Hermans et al. (2021) [6]				
TABLE A	**SR**	**AF**	**Unclassified**	
Positive	0.10%	76.50%	3.20%	
Negative	99.70%	20.90%	94.80%	
Unclassified	0.20%	2.60%	2.00%	
N	115			
N+ (KardiaMobile)	29			
TABLE B	**Positive results**	**Negative results**	**Inconclusive**	
KardiaMobile	0.099370908	0.803825908	0.09680318	TRUE
KardiaMobile + Clinician	0.079920272	0.913952369	0.00612736	TRUE
0				
TABLE C	**Positive results**	**Negative results**	**Inconclusive**	
KardiaMobile	32.96%	59.83%	7.21%	TRUE
KardiaMobile + Clinician	25.22%	74.28%	0.50%	TRUE
TABLE D	**Positive results**	**Negative results**	**Inconclusive**	
KardiaMobile	38	69	8	
KardiaMobile + Clinician	29	85	1	
		Distribution parameters		
	Cases/ Mean	**Alpha**	**Beta**	
Rate of true positive	74.06%	28.141	9.859	
True negative	99.70%	68.793	0.207	
Repeat monitoring after FP	19.44%	7.388	30.612	
Probability of AF positive - inconclusive	3.20%	0.256	7.744	
Probability of AF negative - inconclusive	94.80%	7.584	0.416	
Probability of repeat monitoring after inconclusive	2.00%	0.160	7.840	

A2- We made changes in Table D to make the model flexible to test various prevalence rates:

Version 2.1:

	A	B	C	D	E
40					
41		KardiaMobile	=ROUND(C37*$C$29,0)	=ROUND(D37*$C$29,0)	=ROUND(E37*$C$29,0)
42		KardiaMobile + Clinician	=C38*$C$29	=ROUND(D38*$C$29,0)	=ROUND(E38*$C$29,0)
43		True positive	=C38/C37	=C43*C41	=C41-D43
44		True negative	=C25	=C44*D41	=D41-D44
45		Repeat monitoring after FP	=1- (D25/(1-C43))	=C45*C41	=C41-D45
46		Probability of AF positive - inconclusive	=E24	=C46*E41	=E41-D46
47		Probability of AF negative - inconclusive	=E25	=C47*E41	=E41-D47
48		Probability of repeat monitoring after inconclusive	=1-SUM(C46:C47)	=E41-(SUM(D46:D47))	=E41-D48
49					

Version 3.0:

	A	B	C	D	E
46			**Cases/ Mean**	**Alpha**	**Beta**
47		Rate of true positive	=D24/SUM(D24:D26,C24,E24)	=C47*C43	=C43-D47
48		True negative	=IF($A$36=1,C25,1-(PrevalenceAF*C24/Data!F11)-C26)	=C48*D43	=D43-D48
49		Repeat monitoring after FP	=1- (D25/(1-C47))	=C49*C43	=C43-D49
50		Probability of AF positive - inconclusive	=IF($A$36=1,E24,PrevalenceAF*E24/Data!F11)	=C50*E43	=E43-D50
51		Probability of AF negative - inconclusive	=IF($A$36=1,E25,1-(PrevalenceAF*E24/Data!F11)-E26)	=C51*E43	=E43-D51
52		Probability of repeat monitoring after inconclusive	=1-SUM(C50:C51)	=E43-(SUM(D50:D51))	=E43-D52
53					

We want to report a change in cell C47 in V3.0 that makes minor changes in the estimation of AF positive by KardiaMobile.

Note: There is one switch in cell A36 (V3.0) to undo calculations to V2.1

B: Intermediate calculations for repeat CER and Zio:

B1: We added labels for these two tables, as can be seen below:

Version 2.1:

Repeat AF monitoring rate for CER			
Potential undetected AF	14.363354%	2.465	Zio submission document
	85.636646%	1	
		1.210423137	
	1.210423137	TRUE	
	1	0.178544867	
	0.178544867	0.03187827	
	0.03187827		
Repeat AF monitoring rate for Zio			
Potential undetected AF	14.134783%	2.465	Zio submission document
	85.865217%	1	
		1.207074565	
	1.207074565	TRUE	
	1	0.176072899	
	0.176072899	0.031001666	
	0.031001666		

Version 3.0:

Repeat AF monitoring rate for CER			
Potential undetected AF	14.363354%	2.465	Zio submission document
	85.636646%	1	
		1.210423137	
	1.210423137	TRUE	
	1	0.178544867	
	0.178544867	0.03187827	
	0.03187827		
Repeat AF monitoring rate for Zio			
Potential undetected AF	14.134783%	2.465	Zio submission document
	85.865217%	1	
		1.207074565	
	1.207074565	TRUE	
	1	0.176072899	
	0.176072899	0.031001666	
	0.031001666		

B2: We made changes in the estimation of potential undetected AF for CER and Zio to make the model flexible to test various prevalence rates:

Version 2.1:

Repeat AF monitoring rate for CER		
Potential undetected AF	='USER INPUTS'!I19-'USER INPUTS'!I75	2.465
	=1-C76	1
		=SUMPRODUCT(D76:D77,C76:C77)
	=SUM(C80:C82)	=C79=D78
	1	=(-1+SQRT((1-4*(-D78+1))))/2
	=D80	=C81*D80
	=D81	
Repeat AF monitoring rate for Zio		
Potential undetected AF	=Data!F11-Data!F142	2.465
	=1-C85	1
		=SUMPRODUCT(D85:D86,C85:C86)
	=SUM(C89:C91)	=C88=D87
	1	=(-1+SQRT((1-4*(-D87+1))))/2
	=D89	=C90*D89
	=D90	

Version 3.0:

Repeat AF monitoring rate for CER		
Potential undetected AF	=PrevalenceAF-(('USER INPUTS'!I75*PrevalenceAF)/Data!F11)	2.465
	=1-C80	1
		=SUMPRODUCT(D80:D81,C80:C81)
	=SUM(C84:C86)	=C83=D82
	1	=(-1+SQRT((1-4*(-D82+1))))/2
	=D84	=C85*D84
	=D85	
Repeat AF monitoring rate for Zio		
Potential undetected AF	=PrevalenceAF-(('USER INPUTS'!W62*PrevalenceAF)/Data!F11)	2.465
	=1-C89	1
		=SUMPRODUCT(D89:D90,C89:C90)
	=SUM(C93:C95)	=C92=D91
	1	=(-1+SQRT((1-4*(-D91+1))))/2
	=D93	=C94*D93
	=D94	

C: Intermediate calculations for Holter:

C1: We added labels for Holter information, as can be seen below:

Version 2.1:

	N	115		
	N+ (Holter 7d)	17		
		Positive results	Negative r	Inconclusive
	Holter 24	0.132452174		0.867548
	Holter 48	0.137626087		0.862374
	Holter 7	0.147973913		0.852026
	Holter 24	15	100	
	Holter 48	16	99	
	Holter 7	17	98	

Version 3.0:

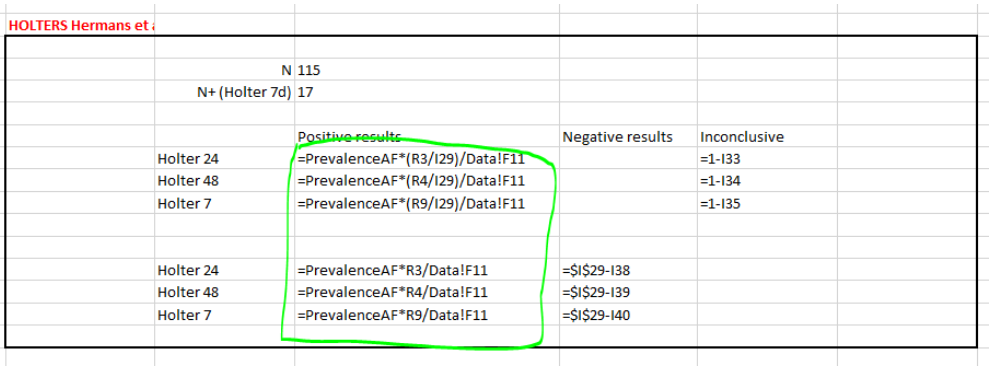
HOLTERS Hermans et al. (2021) [6]				
	N	115		
	N+ (Holter 7d)	17		
		Positive re	Negative res	Inconclusive
	Holter 24	0.132452		0.867548
	Holter 48	0.137626		0.862374
	Holter 7	0.147974		0.852026
	Holter 24	15	100	
	Holter 48	16	99	
	Holter 7	17	98	

C2: We made changes in the estimation of Holter AF+ rates to make the model flexible to test various prevalence rates:

Version 2.1:

	N	115		
	N+ (Holter 7d)	17		
		Positive results	Negative results	Inconclusive
	Holter 24	=R3/I29		=1-I33
	Holter 48	=R4/I29		=1-I34
	Holter 7	=R9/I29		=1-I35
	Holter 24	=R3	=$I$29-I38	
	Holter 48	=R4	=$I$29-I39	
	Holter 7	=R9	=$I$29-I40	

Version 3.0:



HOLTERS Hermans et a				
	N	115		
	N+ (Holter 7d)	17		
		Positive results	Negative results	Inconclusive
	Holter 24	=PrevalenceAF*(R3/I29)/Data!F11		=1-I33
	Holter 48	=PrevalenceAF*(R4/I29)/Data!F11		=1-I34
	Holter 7	=PrevalenceAF*(R9/I29)/Data!F11		=1-I35
	Holter 24	=PrevalenceAF*R3/Data!F11	=$I$29-I38	
	Holter 48	=PrevalenceAF*R4/Data!F11	=$I$29-I39	
	Holter 7	=PrevalenceAF*R9/Data!F11	=$I$29-I40	

D: Intermediate calculations for CER:

D1: We made changes in the estimation of CER AF+ rates to make the model flexible to test various prevalence rates in cells AW24 and AX24:

Version 2.1:

AW24: =IFERROR(VLOOKUP('USER INPUTS'!$I$25,'Inter calculations'!$AU$26:$AX$55,2,FALSE),0)

AX24: = IFERROR(VLOOKUP('USER INPUTS'!$I$25,'Inter calculations'!$AU$26:$AX$55,3,FALSE),0)

Version 3.0:

AW24: = PrevalenceAF*IFERROR(VLOOKUP('USER INPUTS'!$I$25,'Inter calculations'!$AU$26:$AX$55,2,FALSE),0)/Data!F11

AX24: = PrevalenceAF*IFERROR(VLOOKUP('USER INPUTS'!$I$25,'Inter calculations'!$AU$26:$AX$55,3,FALSE),0)/Data!F11

E: Unnecessary data was removed

The following ranges have been removed from V2.1 to clean up the “inter calculation” sheet:

B65:G72

Chart 2

Chart 3

Chart 5

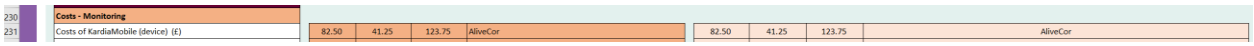
BP2:BU 17

Picture 8

3- Data Sheet

We changed the cost of the KardiaMobile device to 6L in V3.0. Previously, we included the cost of KardiaMobile 1L in V2.1.

Version 2.1:

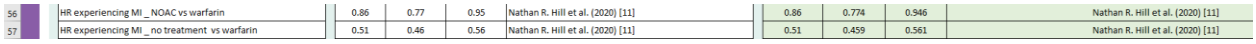


230	Costs - Monitoring								
231	Costs of KardiaMobile (device) (£)	82.50	41.25	123.75	AliveCor	82.50	41.25	123.75	AliveCor

Version 3.0:

229	Costs								
230	Costs - Monitoring								
231	Costs of KardiaMobile (device) (£)	124.00	124.00	124.00	AliveCor	124.00	124.00	124.00	AliveCor

Note: we have noticed a non-correct change in the "Data" sheet after sending V3.0 to EAC. It was happened by mistake. The values in V2.1 are correct. Therefore, we recommend updating two below parameters in V3.0:



56	HR experiencing MI _ NOAC vs warfarin	0.86	0.77	0.95	Nathan R. Hill et al. (2020) [11]	0.86	0.774	0.946	Nathan R. Hill et al. (2020) [11]
57	HR experiencing MI _ no treatment vs warfarin	0.51	0.46	0.56	Nathan R. Hill et al. (2020) [11]	0.51	0.459	0.561	Nathan R. Hill et al. (2020) [11]

We sincerely apologize for any inconvenience it may have caused.

The above changes caused minor changes in the results of the model for KardiaMobile. Please see below the results of KardiaMobile in V2.1 and V3.0.

Version 2.1:

Intervention	KardiaMobile + Clinician	Comparator	Holter 24h
		Time Horizon	5th year after Monitoring period
		Inclusion of Anticoagulants Adverse Events	Yes
		Only initial monitoring comparison	No
Costs (average cost per patient) (£)		Visits after KardiaMobile	Device shows AF positive

	KardiaMobile	Holter 24h	Incremental Δ
Costs of initial AF monitoring (device-related)	8.96	171.20	-162.24
Costs of repeat monitorings (device-related)	0.09	123.89	-123.80
Costs of primary care visits	0.00	0.00	0.00
Costs of secondary care visits	50.28	196.97	-146.69
Costs -Anticoagulants	356.53	241.93	114.60
Costs of stroke	741.91	789.96	-48.06
Costs of MB	0.85	0.64	0.22
Costs of ICH	27.14	18.58	8.56
Costs of MI	23.67	26.18	-2.51
Costs of fatal stroke	47.20	49.78	-2.58
Costs of fatal MB	29.51	24.85	4.66
Costs of fatal ICH	5.57	4.72	0.85
Costs of fatal MI	3.58	3.41	0.18
Costs of two events	1,427.51	1,392.95	34.57
Costs of three events	219.47	211.25	8.22
Costs of four events	6.55	6.39	0.16
Total costs per patient	2,948.82	3,262.69	-313.86

Version 3.0:

Intervention	KardiaMobile + Clinician	Comparator	Holter 24h
		Time Horizon	5th year after Monitoring period
		Inclusion of Anticoagulants Adverse Events	Yes
		Only initial monitoring comparison	No
Costs (average cost per patient) (£)		Visits after KardiaMobile	Device shows AF positive

	KardiaMobile	Holter 24h	Incremental Δ
Costs of initial AF monitoring (device-related)	9.53	171.20	-161.67
Costs of repeat monitorings (device-related)	0.18	123.89	-123.71
Costs of primary care visits	0.00	0.00	0.00
Costs of secondary care visits	50.69	196.97	-146.28
Costs -Anticoagulants	348.12	241.93	106.19
Costs of stroke	745.43	789.96	-44.53
Costs of MB	0.84	0.64	0.20
Costs of ICH	26.51	18.58	7.93
Costs of MI	23.85	26.18	-2.33
Costs of fatal stroke	47.39	49.78	-2.39
Costs of fatal MB	29.17	24.85	4.32
Costs of fatal ICH	5.51	4.72	0.79
Costs of fatal MI	3.57	3.41	0.16
Costs of two events	1,424.98	1,392.95	32.03
Costs of three events	218.88	211.25	7.62
Costs of four events	6.54	6.39	0.15
Total costs per patient	2,941.19	3,262.69	-321.50

Appendix 12

GDPR Consumer FAQ Sheet

AliveCor is committed to protecting our customers by achieving a high standard of data security and compliance in line with GDPR (General Data Protection Regulation) requirements. As our organisation scales, we continue to evolve and adapt our data governance and protection strategies, and strive to provide secure technology services to our customers.

This document is provided as a quick reference to frequently asked questions on how AliveCor handles your data and is not a replacement for AliveCor's official privacy policy, which can be found at alivecor.co.uk/privacy.

How does AliveCor handle my personal information and what are my rights?

Individuals located in the European Economic Area (EEA) have several enumerated rights in how AliveCor handles your personal information. AliveCor acts as Data Controller of your information with very few exceptions (e.g., your healthcare provider generates your Kardia account and provides you access credentials). You should contact AliveCor directly for all requests to exercise your rights under GDPR and for any other concerns you may have about the privacy of your personal information, including:

- The right of access to your personal data;
- The right to correct or rectify any inaccurate personal data;
- The right to restrict or oppose processing of personal data;
- The right to erase your personal data; and
- The right to personal data portability.

To contact an AliveCor Data Controller Representative please email privacy@alivecor.com.

How is my data stored within the EU?

- All data for EEA users are stored securely in the EU (Amazon Web Services in Germany)
- All data is fully encrypted at rest and in transmission
- No data stored in EU data servers will be transmitted to countries outside the EU*
- In standard / premium / KardiaCare mode data is stored in the app locally on the phone and in a secure cloud
- Device and cloud storage can be switched off in the app for users that have additional privacy concerns, where the data will not be stored/backed up in the cloud or locally on your device.

**When you make a request for support, the data you include in that request is sent to AliveCor support staff in the US and used for the sole purpose of providing the support you requested.*

How is my data used?

We rely on user consent as a lawful basis processing personal data for the following purposes:

1. Initial collection of personal data through the Service
2. If users opt-in, providing users with marketing or promotional communications. Users may opt out of such communications at any time by clicking the "unsubscribe" link found within the communications and changing their contact preferences.

Data of European users will not be used for any purpose such as studies or product development.

If you would like to find out more about our privacy and security policy please visit alivecor.co.uk/privacy

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

GID-MT554 KardiaMobile for the ambulatory detection of atrial fibrillation

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Newcastle External Assessment Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **2nd June 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

27 May 2021

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Treskes *et al*. 2020 Excluded based on outcome (BP control); did not address decision problem.	We acknowledge that the primary outcome was BP control. However, the secondary outcomes, were patient satisfaction (general questionnaire and smart technology–specific questionnaire), measurement adherence, all-cause mortality, and hospitalizations for nonfatal adverse cardiac events.	According to this article, KardiaMobile is one of the four included interventions. Although rhythm monitoring is not the primary outcome of this study, patient satisfaction, feasibility and adherence to KardiaMobile for rhythm monitoring were measured and reported as secondary outcomes of this study. Therefore, as per the NICE scope this study should not be excluded.	The Treskes et al. 2020 study was powered to detect a difference in the proportion of patients with regulated BP between intervention and control arms. Therefore the secondary outcomes mentioned (patient satisfaction, measurement adherence, mortality, hospitalisation) are not generalizable to the population included within the final scope. Treskes et al. 2020: patients aged 18 years and older admitted to cardiology department with an acute myocardial infarction. Final scope: Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care. Furthermore KardiaMobile was included within a bundle (including BP monitor, step counter and weight scale). No changes required.

NICE National Institute for Health and Care Excellence

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Halcox *et al.* 2017 Excluded based on screening (population asymptomatic and therefore would not routinely be referred for ECG); did not address decision problem.	Patients included for screening with KardiaMobile if the CHADS-VASc score ≥2. (High risk population).	In this study, patients were included if the CHADS-VASc score ≥2, which means that the target population is at risk of cardiovascular events and therefore, is not considered the same as a healthy population (the likelihood of AF in this population is higher than amongst a normal healthy population). Additionally, screening isn't carried out at a single time-point as each subject is instructed to take twice-weekly recordings over 12 months. This study is also investigating the detection rate of AF by KardiaMobile amongst an at-risk population, in addition to exploring compliance and satisfaction with the device, which are amongst the claimed benefits of the device. Therefore, as per the NICE scope this study should not be excluded as it does address the decision problem.	The Halcox *et al.* 2017 study is a screening study, including a population of asymptomatic adults aged >65 years, with CHADS-VASc score ≥2. This does not represent the population stated within the decision problem of the final scope: Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care. No change required.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Bhavnani *et al.* 2018 Excluded based on mixed intervention, primary outcome was not relevant to decision problem (time to valvuloplasty), outcome includes atrial arrhythmia (atrial fibrillation or atrial flutter, supraventricular tachycardia, or ventricular arrhythmias); did not address decision problem.	The primary outcome was the time to treatment with valvuloplasty or valve replacement over 12-months after the initial mHealth or standard-care assessment. Secondary outcomes included the occurrence of a cardiovascular hospitalization and/or death on follow-up.	Compared to standard care, a shorter duration from enrolment to primary outcome was observed with mHealth (KardiaMobile), with twice as many participants randomized to mHealth undergoing treatment at 90days (20% vs. 10%). On follow-up, 51 subjects (20%) experienced a cardiovascular hospitalization and 3 died (1%). The occurrence of a hospitalization and/or death was lower in the mHealth group than in the standard-care arm. Both primary and secondary outcomes showed the earlier detection of cardiac events by KardiaMobile, which lead to earlier treatment and reduction in hospitalization rate. Therefore, as per the NICE scope this study could be included.	The population within Bhavnani *et al.* 2018 included outpatients (adults, paediatric and pregnant patients) with new or established diagnosis of structural heart disease (included valvular disease, left or right ventricular failure and congenital heart defects). This does not represent the population stated within the decision problem of the final scope: Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care. Furthermore KardiaMobile was included within a bundle (including pocket ECG (VScan), smartphone-connected oximetry and blood pressure monitor, tri-axial activity monitor and PoC fingerstick B-type natriuretic peptide). No change required.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Tarakji *et al.* 2015 Exclude based on comparator (not representative of current NHS care).	This evidence example should be reconsidered	Although the comparator is not of the current standard of care, other relevant outcomes including the ease of use of KardiaMobile was assessed, regardless of the comparator. As per the NICE MTEP methods guide, we believe any study where KardiaMobile is used as comparator or intervention should be included.	The Tarakji *et al.* 2015 study was powered to detect a sensitivity of at least 90% with KardiaMobile when compared to transtelephonic cardiac monitor, which does not represent NHS standard care. No change required.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Soni *et al.* 2019 Excluded based on screening population (would not be referred for ECG).	This evidence example should be reconsidered	This study does not involve a one-time screening of a population, but it is a feasibility study of KardiaMobile with multiple measurement amongst the same population in order to detect AF (i.e., Ambulatory setting). Please see the below statement obtained from the article: "After signing an informed consent, study participants	This does not represent the population stated within the decision problem of the final scope: Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care. No change required.

		were screened for AF using aFDA-approved, single-lead iECG device (Kardia, Alivecor) for a 30 s recording as recommended by the consensus document endorsed by four major international bodies with expertise in heart rhythm. *Participants were screened using the Kardia Mobile device three times over a five-day period".* Regarding this statement, it could be concluded that the screening was not a single time-point study, as the study was investigating the feasibility of AliveCor devices in detecting AF in ambulatory settings.	

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Soni *et al.* 2016 Excluded based on screening population (would not be referred for ECG).	Feasibility of KardiaMobile in detection and prevention of AF in ambulatory setting.	This study does not involve a one-time screening of a population, but it is a feasibility study of KardiaMobile with multiple measurement amongst the same population in order to detect AF	This does not represent the population stated within the decision problem of the final scope: Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG

		(i.e., Ambulatory setting). Please see the below statement obtained from the article: "After obtaining informed consent, a team of trained research coordinators and community health workers enrolled a total of 354 *participants aged 50 years and older and screened them at their residences using Alivecor for 2 minutes on 5 consecutive days over a period of 6 weeks* beginning June, 2015."	monitoring by a clinician in primary, secondary or tertiary care. No change required.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Bose *et al*. 2014 [Abstract] Excluded based on population (would not be referred for ECG, screening) and usability.	By being easy-to-use, scalable, and clinically relevant, novel smartphone enabled ECG recording devices have the potential to radically disrupt the way cardiac screening, monitoring, and diagnosis is performed for both US heart failure patients and patients across the world.	Regarding the study design (abstract only) there is no further information available on population characteristics. However, according to the NICE scope, there is no specification for the included population in the studies, whether they are symptomatic or not.	The exclusion reason stated by the EAC was: *"Excluded based on insufficient data on population (unlikely population would be referred routinely for ECG)."* The Bose *et al.* 2014 study included an unselected group of US patients. Included patients enrolled in clinical trials

		Therefore, any type of population may be included if the outcome of the study is detection of AF by means of the KardiaMobile screening since it's not single time-point.	of the device (15% of population) and those that were prescribed the device for self-monitoring. This does not represent the population stated within the decision problem of the final scope: Adults (18 years or older) with known or suspected atrial fibrillation who are referred for ambulatory ECG monitoring by a clinician in primary, secondary or tertiary care. No change required.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 82, section Population: Prevalence of AF was fixed at 30% and did not change during diagnostic phase even when repeated monitoring was employed.	Please add the following text after the statement: Those who undergo repeat monitoring are a mixture of undiagnosed and no AF cases. As we cannot estimate the proportion of undiagnosed and no AF cases in those who need repeat monitoring, we assumed identical prevalence in the repeated cases, which is applicable for a relatively small proportion of patients.	To provide additional information and avoid any cause of misunderstanding.	The EAC has revised the report for additional clarity as follows: “Prevalence of AF was fixed at 30% and did not change during the diagnostic phase even when 3 rounds of monitoring were employed.” This section of the report describes what the company did. Their justification is available in the company submission (p31, 34) and in the Correspondence Log (p104). No further factual changes to the report are necessary.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 83 The company clarified that in the model all "possible AF" diagnoses from the KardiaMobile device were confirmed by clinician and started treatment on the same day.	Please change it to a clearer statement as follows: The company clarified that in the model all "possible AF" diagnoses from KardiaMobile or any other device (i.e., Holter, CER, and Zio) were confirmed by clinician and started treatment on the same day.	To provide additional information and avoid any cause of misunderstanding.	Page 83 refers to the description of the intervention (i.e. KardiaMobile). However the EAC has now clarified that treatment begins on the same day for comparators also on page 85, in the description of outcomes.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 84 The EAC recognises that patients eligible for implantable cardiac monitoring may have symptomatic episodes that are more than 14 days apart; limiting its value as a comparator to KardiaMobile in this *de novo* model.	This statement needs to be amended.	As clinical experts stated: *implantable cardiac monitoring would be considered in patients with undiagnosed syncope or loss of consciousness.* Both of these two indications are out of the scope of this study. As the company pointed out, patients	Opinion. The EAC continues to query why implantable cardiac monitors feature in the company *de novo* model. The EAC has not excluded Zio as a comparator, however notes there is no direct evidence comparing Zio and KardiaMobile. No change required.

		with loss of consciousness are not eligible to use KardiaMobile. Regarding another statement from the clinical experts: *three stated that low frequency (two or three times a year) or long duration between symptoms (more than two weeks) may require an implantable device.* To understand whether patients have a low frequency (two or three times a year) or long duration between symptoms (more than two weeks), they should undergo primary AF detection by devices with a shorter diagnostic time of 3 years. Therefore, this statement from the EAC is not clinically plausible for the first line of AF ambulatory monitoring. There is no study to compare KardiaMobile versus both Zio and implantable loop recorders. However, the EAC excluded only Zio from the analysis because of no direct comparison. For implantable loop recorders, the EAC has considered it as a model limitation in our analysis. This inclusion/exclusion of comparators appears inconsistent.	

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 85 The EAC considered that repeat monitoring within the diagnosis phase, with different devices, introduced unnecessary complexity and uncertainty (in costs, proportion of use, and time), which could have been removed.	This statement is not consistent with the NICE scope	According to the NICE scope: *Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.* The *de novo* model was developed in a way that can be used to simulate the current diagnostic pathway which is consistent with assumptions used in MTG-52. We think that implementation of repeat monitoring should be taken into account to provide more realistic results.	We have changed the report to clarify that it was the unnecessary complexity and uncertainty which could have been removed from the model: "The EAC considered that the way in which repeat monitoring was included within the diagnosis phase, with different devices and time-dependent probabilities, introduced unnecessary complexity and uncertainty (in costs, proportion of use, and time), which could have been simplified". The company has not provided any robust evidence to support the use of number and combination of devices used in the *de novo* model.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 86 section 9.2.2.	We request a revision on this statement.	The main source of clinical effectiveness data to inform the economic model was obtained from Hermans et al. 2021. According to	The Hermans *et al.* 2021 study provided KardiaMobile to patients post ablation at either their 3, 6 or 12 month follow-up

• The structure of the model was chosen by the company in order to account for time-dependency. However none of the clinical studies which reported time to AF detection or time to treatment (which were included in the company Clinical Submission) were included as inputs in the *de novo* model.		this study, the cumulative distribution of AF detected cases over time shows a non-linear pattern. Therefore, an exponential function was used in the model to distribute AF detected cases over time using λ = 0.62948 so that 100% of AF detected cases (29/115) were identified by day 14. This approach was used due to KardiaMobile's ability of early detection and sending the results of ECG to healthcare professionals instantaneously compared to other comparators. Although the EAC reported the results of multiple studies in which KardiaMobile reduced the time to AF detection (page 64), the EAC did not consider this as an important capability of KM in their cost calculator, leading to an underestimation of potential cost saving associated with earlier detection and intervention to prevent stroke by KardiaMobile, as well as the costs of anticoagulants and associated drug-related side effects.	and patients instructed to use three times daily or when symptomatic for 4 weeks. The reasoning mentioned here was not described by the company in their economic submission and the EAC text holds. An exponential increase in cumulative cases detected over time is an unsurprising consequence of continuous monitoring and may not be due to any complex non-linear phenomenon. Hermans report cumulative yield at three time points and the EAC doubts that the time constant (λ) is estimable to such high precision (1 part in 10000) using only three time points and 29 cases. The time to AF detection identified in this study is not necessarily generalisable to NHS practice. We note on p83 of the Assessment Report that “The clinical experts reported different time intervals between a patient emailing an ECG and it being reviewed: within one working day, three times weekly, once weekly, variable within centre.” The EAC cost calculator has several limitations, including not modelling cumulative yield over time, or the benefits of prescribing medical earlier. However, when used for the Hermans scenario, the full additional yield of KM was accounted for, and management costs were taken over 1 year. Additional benefits due to diagnosis a few days

			earlier are likely to be negligible in comparison to the other limitations of the calculator. No change required.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 86 section 9.2.2. • The company then calculated diagnostic yield in the model for each device using an incorrect and inconsistent approach, see Table 17.	We request a revision on this statement.	Please see our justifications on Issues 18-19.	Opinion. No change required.

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 86 section 9.2.2. • Repeat monitoring was applied in the model for patients with inconclusive results following the first round of Holter monitoring; split between 7-day Holter (90%) and 30-day CER	We think this is a misinterpretation of data from Herman's study.	In section 2.3. Study procedures of the Herman's study, the researchers pointed out that the comparison of Holter monitoring and KardiMobile happened in one of the time-points in the standard of post-AF ablation follow-up care.	Hermans et al. 2021 states: *"As a standard of post-AF ablation follow-up care, outpatient clinic visits including Holter monitoring (minimum 24 h) at three, six* ***and*** *12 months follow-up were performed."* The EAC agrees with the interpretation that in the Hermans study, one of the

(10%). However the diagnostic yield of Holter monitoring (24-hour, 48-hour and 7-day) applied in the *de novo* model was derived from the total number of patients with AF detected at one year from Hermans *et al.* 2019 study, which included 3 rounds of (24-hour minimum) Holter monitoring initiated at 3, 6 and 12 month follow-up outpatient appointments. Using this study as the source of diagnostic yield, the EAC considers it inappropriate to include repeated Holter monitoring following a first round of Holter monitoring.		*As a standard of post-AF ablation follow-up care, [1] outpatient clinic visits including Holter monitoring (minimum 24 h) at three, six and 12 months follow-up were performed. At one of these time points patients were provided with an ACK AliveCor Inc.,Mountain View, CA)* ***simultaneously*** *with Holter and instructed to use the ACK monitor to record 30-s ECG recordings three times daily and in case of symptoms for a period of 4 weeks.* Moreover, in the Results section: *The monitoring strategies (Holter and ACK)were evaluated at 3months follow-up in 74 patients (64.3%), at 6 months follow-up in 16 patients (13.9%), and at 12 months follow-up in 25 patients (21.7%).* Therefore, we think that the Hermans study compares the AF detection rates of KardiaMobile and Holter only in one of the three follow-up points when these two	planned Holter tests for these patients (3, 6, or 12 months) was used as the comparator for KM. The EAC considers that the study design was an experimental opportunity to compare devices, but its comment on p86, section 9.2.2 relates to repeat use of Holter following an inconclusive first round, which is a different scenario. No change required.

		alternatives are used ***simultaneously***. For the EAC's information, Figure 3a shows how KardiaMobile and Holter were used in this study (cells with bolded frames mean period of Holter monitoring over the 28 days study period). Therefore, the repeat Holter monitoring can happen after the initial Holter monitoring. Moreover, in the model we assumed that patients will receive a 7-day Holter monitoring after the first 24h Holter.	

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 89 [Note that the company has included CER and implantable cardiac monitor during repeat testing costings, however it is unclear why these were not considered as direct comparators in the first round of monitoring].	Please consider the removal of this comment based on our further discussions during our meetings and the further justification	For further justification, please see study by Reed et al. 2019, background section: *If patients are referred to cardiology services for assessment, investigation usually starts with a Holter monitor but non-compliance and lack of extended monitoring*	Opinion. No justification for inclusion of CER and implantable was provided by the company. No change required.

		reduces diagnostic yield to less than 20% [11]. Traditional event recorders, external continuous loop recorders and implantable loop recorders are expensive and not recommended for a patient group who rarely have malignant arrhythmias and may have prolonged periods between episodes.	

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 90 Table 17 Holter with different duration.	We think the EAC interpretation from the AF detection rate is based on a misunderstanding from the Hermans study. We request a revision of this interpretation.	In section 2.3. Study procedures of the Herman's study, the researchers pointed out that the comparison of Holter monitoring and KardiMobile happened in one of the time-points in the standard of post-AF ablation follow-up care. *As a standard of post-AF ablation follow-up care, [1] outpatient clinic visits including Holter monitoring (minimum 24 h) at three, six and 12 months follow-up were performed. At one of these time points patients were provided with an ACK*	On page 90, Table 17, the EAC has explained the method used by the company to derive its diagnostic yields, including from the Hermans study. We agree with the company's interpretation of the study design (see also our response to issue 14) but that is unrelated to the critique in the table (that the assumption of the diagnostic yield is incorrect as it conflates separate studies). No change required.

		AliveCor Inc., Mountain View, CA) ***simultaneously*** *with Holter and instructed to use the ACK monitor to record 30-s ECG recordings three times daily and in case of symptoms for a period of 4 weeks.* Moreover, in the Results section: *The monitoring strategies (Holter and ACK)were evaluated at 3months follow-up in 74 patients (64.3%), at 6 months follow-up in 16 patients (13.9%), and at 12 months follow-up in 25 patients (21.7%).* Therefore, we think that Hermans study compares the AF detection rates of KardiaMobile and Holter only in one of the three follow-up points when these two alternatives are used ***simultaneously***. For the EAC's information, Figure 3a shows how KardiaMobile and Holter were used in this study (cells with bolded frames mean period of Holter monitoring over the 28 days study period.) Therefore, the statement of:	

		The study reported that 14.8% (17/115) of patients had AF detected by minimum 24-hour Holter monitoring (conducted at 3-, 6- and 12-month follow-up). is not correct. Regarding the approach that we used to estimate the proportion undiagnosed AF, we would like to point out that ultimately there would not be any difference between the estimation of difference in undiagnosed AF between the de novo model and simple model by EAC. For example, the EAC estimated **10.4%** AF missed (page 112, Table 24). In the de novo model, the relative undetected AF would be identical: KM: 30.4% -25.2% = 5.2% Holter (all) = 30.4% - 14.8% = 15.6% difference = 15.6% - 5.2% = **10.4%** Therefore, there is no difference between models in the estimation of AF missed proportion. Regarding different AF detection rates obtained from Hermans *et al.* 2021, we would like to provide more explanation. As Figure 3a in the Hermans study shows, the duration of Holter monitoring is between	

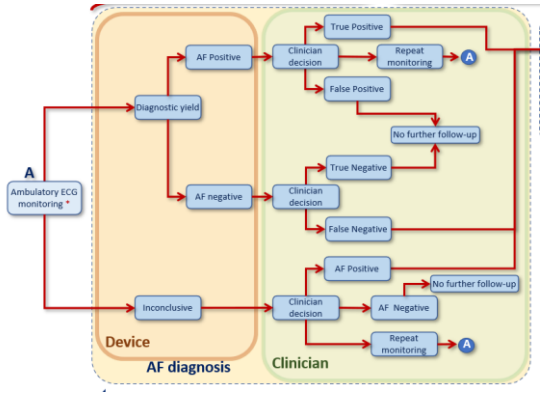
		patients. Therefore, we distributed the total AF detected cases proportionality between three Holter durations of 24h (89.6%), 48h (3.5%), and 7days (7.00%) [please see Table 1 in Hermans study]. In the next step, we estimated cumulative AF detection for Holter 48h (89.6+3.5%) and Holter 7d (89.6+3.5%+7.0%).	

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 90 Table 17 KardiaMobile+Clinician A total of 7,838 ECG recordings from 115 patients were captured in the Hermans *et al.* 2021 study; the company excluded 49 which were categorised as unreadable by the Kardia app. Of the remaining 7,789 ECG recordings, 9.9% were possible AF, 80.4% were normal, 9.7% were unclassified. Of the 774 ECG recordings that were deemed possible AF by	We request a revision in the interpretation.	We understand the EAC concern on our approach. However, we have some justifications on what we have done for KardiaMobile. First, the results of Hermans et al. 2021 shows that there was no significant difference between total tracings sent in patients with and without AF recurrence (Table 2).	Chi squared analysis using data from this table tested for evidence of a difference in the number of ECG traces submitted by the AF and no AF groups by monitoring time, and found no evidence to reject the null (there is no difference between AF and no AF in usage over time). The additional chi-squared analysis table does not provide information to demonstrate how many of the ECG traces had AF recurrence detected by KardiaMobile (e.g. one patient could have had 50 “possible AF” results); it does not address the

KardiaMobile, only 592 were confirmed positive following clinical review; therefore KardiaMobile categorised 1.3074 (774/592) more ECG recordings as AF than the clinician. The company have applied this scaling factor (from ECG recordings) to determine the proportion of patients who would have been classed as AF if the Kardia app determination had been used only; 1.3074*(29/115) = 32.96%. This approach is inappropriate as repeated ECGs (mean of 68 per patient) are not independent. The company has then distributed the remaining patients (67.04%) to normal and unclassified groupings using the ECG proportions: 59.83% normal sinus, 7.21% unclassified. The company then combined the proportion of positive (possible AF, 32.96%) and negative (normal sinus, 59.83%) results to get an overall diagnostic yield of 92.79%. The EAC cannot explain why both positive and negative results contributed to the diagnostic yield of KardiaMobile but that only positive results contributed to		**Table 2** AliveCor Kardia® usage statistics. Bold text indicated a statistically significant difference with a p-value less than 0.05. Variable | Study group (n = 115) | | | *p*-Value All patients | Patients without AF recurrences (n = 86) | Patients with AF recurrences (n = 29) Days from enrollment to last tracing Median [IQR] | 28.0 [21.0–32.0] | 28 [20.8–32.3] | 28 [19.0–32.0] | 0.689 ≥41 | 6 (5.2%) | 5 (5.8%) | 1 (3.4%) | 1.000 31–40 | 34 (29.6%) | 25 (29.1%) | 9 (31.0%) | 0.819 21–30 | 47 (40.9%) | 35 (40.7%) | 12 (41.4%) | 1.000 11–20 | 21(18.3%) | 16 (18.6%) | 5 (17.2%) | 1.000 0–10 | 7 (6.1%) | 5 (5.8%) | 2 (6.9%) | 1.000 Total tracings sent Mean ± SD | 68.2 ± 28.2 | 67.0 ± 28.3 | 71.7 ± 28.1 | 0.430 ≥101 | 12 (10.4%) | 8 (9.3%) | 4 (13.8%) | 0.494 81–100 | 29 (25.2%) | 20 (23.3%) | 9 (31.0%) | 0.461 61–80 | 32 (27.8%) | 25 (29.1%) | 7 (24.1%) | 0.811 41–60 | 25 (21.7%) | 21 (24.4%) | 4 (13.8%) | 0.302 21–40 | 9 (7.8%) | 5 (5.8%) | 4 (13.8%) | 0.227 0–20 | 8 (7.0%) | 7 (8.1%) | 1 (3.4%) | 0.677 As it is shown in the table, there is no significant difference in mean and per group of ECG frequencies between patients with and without AF. Additionally, we have done a Chi-square test over different tracing groups and the results still showed that there is no difference between patients with and without (AF negative + inconclusive) AF recurrences. Below, there is a R code for the Chi-square test: X <- matrix(c(8, 20, 25,21,5,7,4,9,7,4,4,1), ncol = 2) dimnames(X) <- list(c(">=101","81-100", "61-80","41-60","21-40","0-20"), c("Patients without AF recurrences (n = 86)", "Patients with AF recurrences (n = 29)")) chisq.test(X)$p.value	question of lack of independence described by the EAC on page 90, Table 17. No change required.

the diagnostic yield of comparators. The EAC considers this approach fundamentally flawed and inconsistent across study arms.		Patients without AF recurrences (n = 86) Patients with AF recurrences (n = 29) >=101 8 4 81-100 20 9 61-80 25 7 41-60 21 4 21-40 5 4 0-20 7 1 p.value= 0.4793 Therefore, we could assume that the ECGs were equally distributed among patients with or without detected AF (Bayes' theorem). We used this approach to estimate the proportion of patients who were candidates for subsequent monitoring. Otherwise, the probability of AF positive (the most important input parameter) in the de novo model is identical with the cost calculator developed by the EAC. Taking this approach was necessary as we had to estimate what proportion of AF positive cases detected by KardiaMobile need to receive a subsequent monitoring procedure. Regarding the “Diagnostic yield,” only KardiaMobile can predict the results (positive, negative, and inconclusive) in the “Device” area of the below Figure. In the case of other devices, a clinician detects the positive cases, and non-positive cases might be negative or be a candidate for subsequent monitoring. To keep the model structure identical across arms, we assumed that non-AF positive cases, other than the KardiaMobile arm, remain inconclusive until a clinician decides who is	

		negative and should receive subsequent monitoring in the below model structure.  	

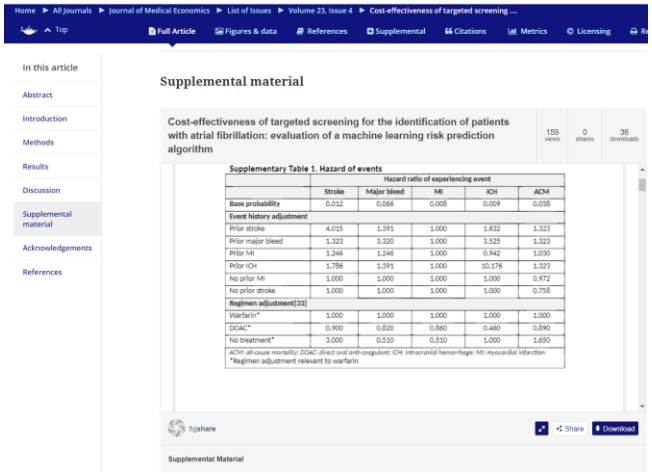
Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 93 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.	We think that this could be non-relevant source of information for the UK	Having looked at the SPARC tool, it seems that the data sources that were used are mostly focussed on populations other than UK population. For example, for the estimation of CHADS2 & CHA2DS2-VASc, the tool used a Danish and relatively old study (Olesen et al. 2011) and for the estimation of Stroke+TIA risk without AF, the tool used another study from Alberta. While the data provided by Hill et al. 2020 was sourced to a systematic review and meta-analysis by Lopez et al. 2017	Opinion. Source provided by expert. No change required.

		including 23 randomised trials involving 94,656 patients. (Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis | The BMJ) Another source of data used by Hill et al. 2020 was a UK systematic review, meta-analysis and cost-effectiveness analysis by Welton et al. 2017, entitled: Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis https://pubmed.ncbi.nlm.nih.gov/28629510/ Therefore, we think that input data used in the de novo model is more robust than the data provided in the cost calculation tool.	

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 93 Additionally the company stated in the Economic Submission that the hazard ratios for	Apologies, we thought it would be easier to access the source data and justification as follows	Please use the following link: Full article: Cost-effectiveness of targeted screening for the identification of patients with	This is different to the reference Hill et al. included in the company Economic Submission and Economic model:

adverse events (stroke, major GI bleed, MI or intracerebral haemorrhage ICH) for given medication regimes were primarily based on data from Hill *et al*. 2020. The EAC asked the company to clarify this further; the company responded with a screenshot of a supplementary table containing the values used in the model and directed the EAC to the supplementary material. Having checked this source, the EAC remained unable to verify the parameters.		atrial fibrillation: evaluation of a machine learning risk prediction algorithm (tandfonline.com) then select “Supplement material” from the left menu.  	Company Economic Submission: 15. Hill, NR., Sandler, B., Bergrath, E., et al. A Systematic Review of Network Meta-Analyses and Real-World Evidence Comparing Apixaban and Rivaroxaban in Nonvalvular Atrial Fibrillation, 2020. Clinical and Applied Thrombosis/Hemostasis (2020), 26:1-10. De novo model: 11. Hill, NR., Sandler, B., Bergrath, E., et al. A Systematic Review of Network Meta-Analyses and Real-World Evidence Comparing Apixaban and Rivaroxaban in Nonvalvular Atrial Fibrillation, 2020. Clinical and Applied Thrombosis/Hemostasis (2020), 26:1-10.

NICE National Institute for Health and Care Excellence

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 98 In MTG52, the EAC estimated a mean of 1.465 additional tests were required for the group of patients requiring test repetition. The company has included 2.465 in their calculation to derive rate of repeat monitoring for Zio. The EAC queried this with the company and gained the following response: *"To estimate the proportion of patients who need test repetition, we have used a weighted average of one test for the proportion of patients who have AF and have been detected by Zio, and those who don't have AF. Moreover, 1+1.465 tests for those who have AF but are not detected in the initial test (i.e. 1-prevalece-AF+[sic]). In the case of Zio, the weighted average of number of monitoring would be 1.21. In the next step, we converted this value, considering two time of repeat monitoring (a quadratic equation). Therefore, we estimated a 17% chance of repeat monitoring in the case of*	We are sorry, we thought we provided a clear explanation using the term of quadratic equation.	Assuming we have a population that used Zio and X% of this population are candidates for another AF monitoring (round 2). After the second round, again we will have X% of X% for another AF monitoring (round 3): Therefore: (proportion of 3rd AF monitoring) X^2 + (proportion of 2nd AF monitoring) X + proportion of 1st AF monitoring) 1 = Weighted average of AF monitoring (1.207) $X^2 + X + 1 = 1.207$ Then: X= (-1+SQRT((1-4*(-1.207+1))))/2 https://en.wikipedia.org/wiki/Quadratic_equation X= 0.176 = 17.6% We hope this helps.	Thank you. The EAC is able to solve quadratic equations, but could not follow the argument used, which was not given in the original submission. We have corrected the report to change "verify" to "validate". Please also see our response to Issue 21, below.

Zio". The EAC was unable to verify this calculation.			

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 98 Rate of repeat monitoring after CER 0.179 The company has taken the same approach as above to derive repeat monitoring for CER. However the EAC is unclear how additional tests of Zio can inform the repeat monitoring of CER, therefore considers this an invalid assumption.	The rate of additional tests (1.465) is not only for Zio. This statement needs to be revised.	MTG52, page 98: The probability of test repetition is used in both cardiology and stroke models. It was estimated using analysis of HES data conducted by the company. The company's model estimated a mean of 1.44 additional tests performed in the group of patients who undergo test repetition. From the HES data provided by the company, the EAC calculates 1.465 additional tests for the 27% of patients who undergo more than one test within 12 months. The HES data presenting repeat testing incorporates various tests including 24 and 48 hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring (NICE TA593).	Thank you. This was not clearly described in the economic submission and we have now deleted the final sentence. Rate of repeat monitoring after CER 0.179 The company has taken the same approach as above to derive repeat monitoring for CER. ~~However the EAC is unclear how additional tests of Zio can inform the repeat monitoring of CER, therefore considers this an invalid assumption.~~ We note that in MTG52, the EAC for the Zio assessment, go on to say: "The EAC has some reservations regarding an assumption that an average of 1.389 tests are undertaken per patient for symptomatic patients in the cardiology model or for patients in the stroke models. The HES data provided by the company refers to a group of procedures including exercise

		Therefore, we do not think that rate of 1.465 belongs to only Zio.	stress tests. The HES data presenting repeat testing incorporates various tests including 24 and 48 hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring (NICE TA593). This may artificially increase the estimated number of repeated Holter tests, for example according to the NICE CG109 people who have experienced syncope during exercise, need to undergo exercise ECG monitoring as part of their diagnostic routine. The EAC was unable to source a more reliable estimate of the number of repeat tests but believes the true figure may be lower than a mean of 1.389 investigations per patient." The EAC remains unable to fully validate the value used for repeat testing.

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 110 – section 9.4.1 • All CHA2DS2-VASc scores are given medication;	This assumption is not consistent with the NICE clinical guidelines.	According to the NICE guideline [NG196] Published: 27 April 202: 1.6.7. Do not offer stroke prevention therapy with anticoagulation to people aged under 65 years with atrial fibrillation and no risk factors other than their sex (that is, very low risk of stroke equating to a	Thank you. This is a limitation of the cost-calculator which was developed rapidly in order to assist the committee. It is only relevant when modelling CHA2DS2-VASc score 1 and 0 (noting that these would be unlikely to be referred for ECG monitoring in line with final scope population). We have added

		CHA2DS2-VASc score of 0 for men or 1 for women). This assumption overestimate costs of anticoagulants when 25% of the population have CHA2DS2-VASc less than 2 (NG196, 2021 (page 179)).	a footnote to Table 26, p115 to note this caveat.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 110 – section 9.4.1 • All KardiaMobile ECGs are reviewed by a clinician.	This is a very conservative scenario and we suggest it is not considered in the base-case analysis.	Using this assumption, the EAC team assumes that there is no difference between KardiaMobile and the other devices, which is ignoring the fact that unlike all the other devices, KM has an AI algorithm that can give the initial report with high specificity. It is unrealistic to assume all the negative cases will need to be seen by clinician.	This assumption is in line with the device instructions for use which explicitly states that the output of KardiaMobile cannot be used as a clinical diagnosis, and that clinical interpretation is required. No change required.

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 114, Table 25	This study is not relevant in the cost analysis, therefore should not be used	Firstly, According to Reed et al. 2019, the intervention arm consists of standard care **plus** the use of a	The study by Reed et al. 2019 was one of the five economic studies included by the company within their economic

Reed *et al.* 2019 UK (n=240).		smartphone-based event recorder. It means that the obtained AF detected rate in this study is a mixed outcome of two different procedures. Therefore, the results of the intervention arm in this study should not be used for KardiaMobile alone and compared with the results of other studies when other studies included only KardiaMobile in their intervention arm. Secondly in this study the protocol of AF detection by KardiaMobile (number of monitoring per day) is not reported. Moreover, the time dependent AF detection between arms was not reported either. It is not clear for us how the EAC team reached the cost estimation of £52.97 and £21.42 for KardiaMobile + Holter and Holter alone[1] respectively, when the difference in AF detection is similar with Narasimha et al. 2018 (6.5 vs. 6.1). 1. This is based on the EAC interpretation from the Reed et al. 2019 on page 113.	within their economic submission (section 2 “Details of relevant studies”). Reed et al. 2019 was an RCT conducted in UK NHS hospital setting, included in clinical submission as directly relevant to the decision problem. No change required.

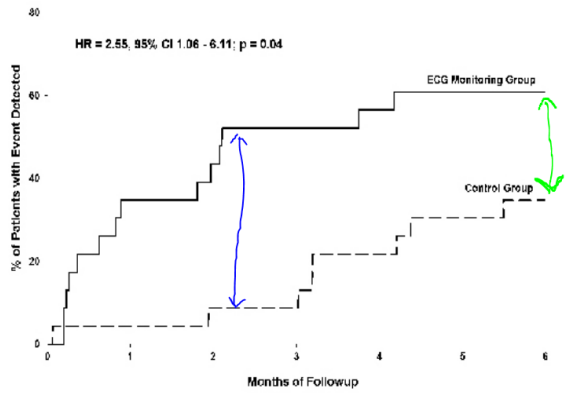
Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 114, Table 25 Goldenthal *et al.* 2019 US (n=233).	The results of the analysis should be interpreted with caution for cost analysis due to the lower frequency of ECG recordings leading to a potential reduction in diagnostic yield	The ECG recording frequency is related to the diagnostic yield. Other studies such as Hermans used more realistic schedule of recordings (3 ECGs a day vs 1 ECG a day). Therefore, there is a chance of underestimation of AF detection by KM. Patients were instructed to record a daily ECG and additional ECGs whenever they experienced symptoms perceived to be associated with an atrial arrhythmia.	We have been clear that the EAC cost calculator is limited in its scope and was required due to the opacity of the company's model. The scenario calculations are based on the crude reported increased rates of detection of AF in each study. We have appraised each study individually and noted in several places that the study designs, populations, intervention (use case) and comparators differ. No change required.

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 114, Table 25 Hickey *et al.* 2017 US (n=46).	The results of this analysis used in this study should be interpreted with caution.	Firstly, The ECG recording frequency is related to the diagnostic yield. Other studies such as Hermans used more realistic schedule of recordings (3 ECGs a day vs 1 ECG a day)	Please see the response to Issue 25 No change required.

		Therefore, there is a chance of underestimation of AF detection by KM. Secondly, there is no term of “standard care” in this study, and we do not know how the EAC recognized the comparator in the US setting and estimated associated cost. Thirdly, the EAC's linear modelling approach of AF detection underestimates the impact of KardiaMobile on AF detection and reduction of stroke costs. For example, the EAC underestimates the impact of KardiaMobile by selecting the latest difference in AF detection point (month 6) instead of using the hazard ratio between two Kaplan-Meier curves in Figure 2 in Hickey et al. 2017. We have implemented time-dependent probabilities in the detection phase to avoid such errors.	

		 Figure 2: Kaplan-Meier Curves for AF/AFI Detection	

Issue 27

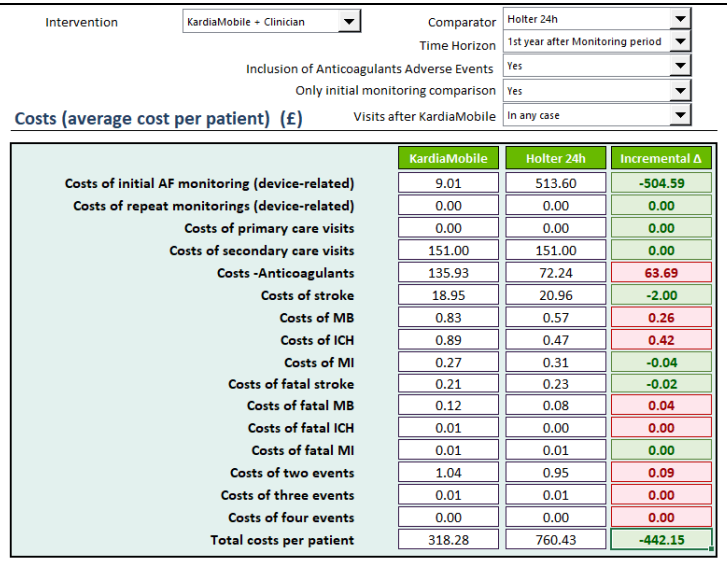
Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 114, Table 25 Narasimha *et al.* 2018 US (n=33).	The results of this analysis used in this study should be interpreted with caution.	Firstly, The ECG recording frequency is related to the diagnostic yield. Other studies such as Hermans used more realistic schedule of recordings (3 ECGs a day vs symptom triggered only) Therefore, there is a chance of underestimation of AF detection by KM. Secondly, there is no term of "standard care" in this study, and	Please see our response to Issue 25. No change required.

		we do not know how the EAC recognized the comparator in the US setting and estimated associated cost. Narasimha et al. 2018 reported a range from 14-30 days for KardiaMobile use in which roughly 30-35 tracings/patient were collected. However, in Herman's study, the total tracing set was 68.2 ± 28.2 per patient.	

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 112 The cost calculation for the scenario based on Hermans *et al*. (2021) which compared KardiaMobile to three rounds of (minimum 24-hour) Holter monitoring is described in Table 24.	We think this is a misinterpretation of data from the Herman's study. It seems that the EAC overestimated costs of Holter (×3) in their analysis which is not correct.	In section 2.3. Study procedures of the Herman's study, the researchers pointed out that the comparison of Holter monitoring and KardiaMobile happened in one of the time-points in the standard of post-AF ablation follow-up care. *As a standard of post-AF ablation follow-up care, [1] outpatient clinic visits including Holter monitoring (minimum 24 h) at three, six and 12 months follow-up were performed. At one of these time points patients were provided with an ACK AliveCor Inc.,Mountain View, CA)* ***simultaneously*** *with Holter and instructed to use the ACK monitor to record 30-s ECG recordings three times daily and in case of symptoms for a period of 4 weeks.* Moreover, in the Results section:	Please see our response to Issue 14.

		The monitoring strategies (Holter and ACK)were evaluated at 3months follow-up in 74 patients (64.3%), at 6 months follow-up in 16 patients (13.9%), and at 12 months follow-up in 25 patients (21.7%). Therefore, we think that Hermans study compares the AF detection rates of KardiaMobile and Holter only in one of the three follow-up points when these two alternatives are used ***simultaneously***. For the EAC's information, Figure 3a shows how KardiaMobile and Holter were used in this study (cells with bolded frames mean period of Holter monitoring.) When we multiplied costs of Holter 24h by three in the de novo model, the results were similar to the results of the EAC's cost calculation.	



Intervention: KardiaMobile + Clinician
Comparator: Holter 24h
Time Horizon: 1st year after Monitoring period
Inclusion of Anticoagulants Adverse Events: Yes
Only initial monitoring comparison: Yes
Visits after KardiaMobile: In any case

Costs (average cost per patient) (£)

	KardiaMobile	Holter 24h	Incremental Δ
Costs of initial AF monitoring (device-related)	9.01	513.60	-504.59
Costs of repeat monitorings (device-related)	0.00	0.00	0.00
Costs of primary care visits	0.00	0.00	0.00
Costs of secondary care visits	151.00	151.00	0.00
Costs -Anticoagulants	135.93	72.24	63.69
Costs of stroke	18.95	20.96	-2.00
Costs of MB	0.83	0.57	0.26
Costs of ICH	0.89	0.47	0.42
Costs of MI	0.27	0.31	-0.04
Costs of fatal stroke	0.21	0.23	-0.02
Costs of fatal MB	0.12	0.08	0.04
Costs of fatal ICH	0.01	0.00	0.00
Costs of fatal MI	0.01	0.01	0.00
Costs of two events	1.04	0.95	0.09
Costs of three events	0.01	0.01	0.00
Costs of four events	0.00	0.00	0.00
Total costs per patient	318.28	760.43	-442.15

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 112, Table 23: Risk reduction to stroke in treated AF : 68%.	Risk reduction associated with NOACs should be included in the input table.	If the EAC model includes only the risk reduction associated with warfarin, the relative impact of NOACs on reduction of stroke has been ignored. This issue will lead to an underestimated efficacy of KardiaMobile when relative risk of stroke in patients who used NOAC is 0.51 compared to warfarin	Thank you. This is a limitation of the cost-calculator which we have noted on page 117.

		according to Nathan R. Hill et al. (2020).	

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 112, Table 23: Cost of anticoagulation (including bleeding) £368.05.	This is an incorrect estimation of overall costs of anticoagulation.	NG196, 2021 (Table 10 -page 90) represents the costs of anticoagulants. It seems that the EAC assumes an identical market share for all anticoagulants. (Warfarin: £210.26+ Dabigatran £400.89 + Edoxaban £400.89 + Rivaroxaban £427.35 + Apixaban £400.85 Avg= £1840.24/5= £368.05) This could not be a correct assumption as we know that anticoagulants have different market shares. Moreover, the above costs represent costs of anticoagulants and Venous thromboembolism	Thank you. This is a limitation of the cost calculator which was developed rapidly due to the opacity of the company's model. We acknowledge that its limitations are transparent. The EAC does not hold sales data to determine weighted average costs. We have clarified that the costs include Venous thromboembolism (VTE) acute treatment in table 23.

		(VTE) acute treatment over six months and not annually. Lastly, it is unclear what (including bleeding) cost means in Table 23 from the EAC report.	

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 123 The largest uncertainty remaining is the magnitude and confidence interval of cost-saving if KardiaMobile was implemented across the NHS. This could be addressed in a simplified model, developing upon the cost calculator created by the EAC, or those developed for previous technology assessments of AF diagnostic devices, and including probabilistic sensitivity analysis to assess the impact of varying diagnostic yield, uncertainty in costs of AF management and risk of stroke.	We appreciate the EAC team for the critical review of the KardiaMobile submission. However, we think that the results of both models are similar, so we think that EAC can rely on the probabilistic analysis of the de novo model if the values change to the recommended values by the EAC.		Opinion. No change required.

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 13 1.2 Intervention The company previously marketed the KardiaBand device; a smart band designed for use with an Apple smart watch. However, given the different mode of use (wearable) and that KardiaBand was removed from sale in 2019, the EAC has excluded evidence that includes KardiaBand as the intervention.	KardiaBand evidence should also be included as the intervention	Although KardiaBand is a wearable the mode of use is the same as KardiaMobile Single lead. To take an ECG the Kardia App needs to be opened and a user must hold the electrode to generate a single lead ECG the same as KardiaMobile. The Apple Watch strap is fitted with a KardiaMobile electrode (in theory a folded KardiaMobile), for example back electrode contacts the left arm the top electrode is held by the right arm to give an equivalent lead one ECG. In this case the mode of use is the same although the Kardia app is opened within the Apple Watch only rather than the Smart device.	The accessibility and use of the KardiaBand is not the same as KardiaMobile therefore results not generalisable. No change required.

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 13 The URL link to the compatible smartphone or tablet computer is incorrect and goes to a third party	The correct link to the AliveCor compatibility list is Compatible smartphone or tablet https://alivecor.zendesk.com/hc/en-us/articles/1500000449521-Compatibility	The URL link to the compatible smartphone or tablet computer is incorrect and goes to a third party	Many thanks for pointing this out the hyperlink has been updated in the report.

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Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 18 The EAC considers that the proposed work flow (described in Figure 1) is dependent upon the patient emailing the ECG recording. This proposed process could introduce bias through missing data (for example patient may forget to send email), and the security of the approach should be considered (as the ECG trace contains patient identifiers and is emailed from the patients personal email as an attachment).	The EAC considers that the proposed work flow (described in Figure 1) is dependent upon the patient emailing the ECG recording (this is one option of sharing the ECG manually, KardiaPro can be used so ECGs are sent automatically to a physician accessible portal, this is a premium function). This proposed process could introduce bias through missing data (for example patient may forget to send email, unless KardiaPro is used and it is GDPR compliant), and the security of the approach should be considered (as the ECG trace contains patient identifiers and is emailed from the patients personal email as an attachment).	The proposed work flow references one option for sharing the ECG only eg email. Although this is the most popular method, KardiaPro is available and once a patient is connected all ECGs are sent automatically to the physician portal where they can access	KardiaPro was not included in the submission. Clinical context has been restricted to the technologies included in the clinical submission (KardiaPro was not included by the company). No change required.