LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

The clinical and cost effectiveness of lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single-time point testing in primary care [DAP39]

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LIST OF ABBREVIATIONS

AF	atrial fibrillation
AUC	area under the curve
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Database of Controlled Trials
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
EAG	External Assessment Group
ECG	electrocardiogram
ESC	European Society for Cardiology
HTA	Health Technology Assessment
MDT	multidisciplinary team
NICE	National Institute for Health and Care Excellence
NOAC	newer oral anticoagulant
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial
ROC	receiver operating characteristic

1 PLAIN ENGLISH SUMMARY

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia (abnormal heart rate). People with AF are more likely to have a serious stroke or die compared with people without the condition. Many people go to their general practitioner (GP) with signs and symptoms commonly associated with AF such as feeling dizzy, being short of breath, feeling tired and having heart palpitations. At the moment, GPs check for AF by taking the patient's pulse by hand. If the GP thinks the patient might have AF, a 12-lead ECG is arranged. 12-lead ECGs use several pads stuck to the patient's arms, legs and chest to measure how the heart is working. Sometimes a 12-lead ECG can be carried out in the GP practice on the same day as the original appointment. However, it may not be possible to get an appointment on the same day or the GP practice may not have its own 12-lead ECG. If the 12-lead ECG cannot be carried out on the same day, patients may have to travel to be tested and the arrhythmia may have subsided by the time the 12-lead ECG is recorded.

Lead-I (i.e. one lead) ECGs can be an alternative to 12-lead ECGs for testing whether people may have AF. Lead-I ECGs are handheld devices with software that can detect AF. Testing patients using lead-I ECG devices during their GP appointment may mean that AF is detected earlier than if they were referred for 12-lead ECG. If that is the case, then using lead-I ECG devices in the GP surgery will allow people to receive treatment for their AF earlier than they do at the moment.

This project will review the existing scientific evidence and will assess the cost effectiveness (costs and benefits) associated with the use of lead-I ECGs to detect AF in people going to their GP with signs and symptoms of AF.

2 DECISION PROBLEM

2.1 Aim of the assessment

The aim of this assessment is to evaluate whether the use of lead-I electrocardiogram (ECG) devices to detect atrial fibrillation (AF) in people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse represents a cost effective use of NHS resources compared with manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy.

2.2 Target condition

AF refers to a disturbance in heart rate (arrhythmia) that is caused by abnormal electrical activity in the upper chambers of the heart (atria).[1] The arrhythmia reduces the efficiency of the heart to move blood into the ventricles, increasing the risk of blood clots and consequent stroke.

2.2.1 Epidemiology

AF is the most common cardiac arrhythmia.[2] The estimated prevalence of diagnosed AF in England is 1.8%.[3] However, AF can be asymptomatic and it is likely that 1.8% is an underestimate of the true prevalence.[4] Published estimates from Public Health England[5] suggest that the prevalence of AF in England is approximately 2.5%, equating to 1.4 million people living with AF.

The prevalence of AF increases with age and a higher proportion of men than women live with the condition (2.9% and 2.0%, respectively).[5] Although the prevalence of AF is lower in women than in men, women have greater mortality than men due to AF-related strokes. AF is associated with conditions such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus and kidney disease.[6]

2.2.2 Types of atrial fibrillation

Three types of AF (based on presentation and duration of the arrhythmia) are described in Table 1.

Table 1 Types of atrial fibrillation

Type of AF	Description
Paroxysmal (intermittent)	Intermittent episodes that usually last less than 7 days and stop without treatment
Persistent	Episodes lasting longer than 7 days (which do not terminate without treatment)
Permanent	Present all the time

Source: NICE CG180[2]

AF can be categorised as valvular or non-valvular for the purposes of choosing the most suitable treatment. Categorisation as valvular or non-valvular refers to the underlying condition causing AF (i.e. whether there is valve disease present or not) rather than the duration of AF episodes. Both valvular and non-valvular AF can be paroxysmal, persistent or permanent.

2.2.3   Impact of atrial fibrillation

Patients with AF may experience palpitations, dizziness, shortness of breath and tiredness. However, AF can be asymptomatic and identified only when people attend medical appointments for conditions other than AF. Untreated AF is associated with a fivefold increase in the risk of stroke and a threefold increase in the risk of heart failure.[7] Strokes associated with AF may be more severe than strokes that are not related to AF.[8]

2.2.4 Current diagnostic and treatment pathways

The National Institute for Health and Care Excellence (NICE) clinical guideline CG180[2] provides recommendations for the diagnosis and management of AF. An update of CG180 is planned.

Diagnosis of atrial fibrillation

In CG180,[2] NICE recommends the use of manual pulse palpation to detect the presence of an irregular pulse that may indicate underlying AF in people who have symptoms such as, breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, previous stroke or suspected transient ischaemic attack.

Clinical experts commented during the scoping stage for this assessment that people presenting with a stroke or transient ischaemic attack would have ECG testing for atrial fibrillation in secondary care and are outside of the scope of an assessment focussing on primary care.

If AF is suspected because of an irregular pulse, it is recommended in CG180[2] that the diagnosis should be confirmed based on the results of an ECG. People who have suspected paroxysmal AF that is not detected by the ECG should be monitored with either a 24-hour ambulatory monitor, or an event recorder ECG. People with confirmed AF may also undergo echocardiography to further inform the management of their condition. The current diagnostic pathway for people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse is depicted in Figure 1.
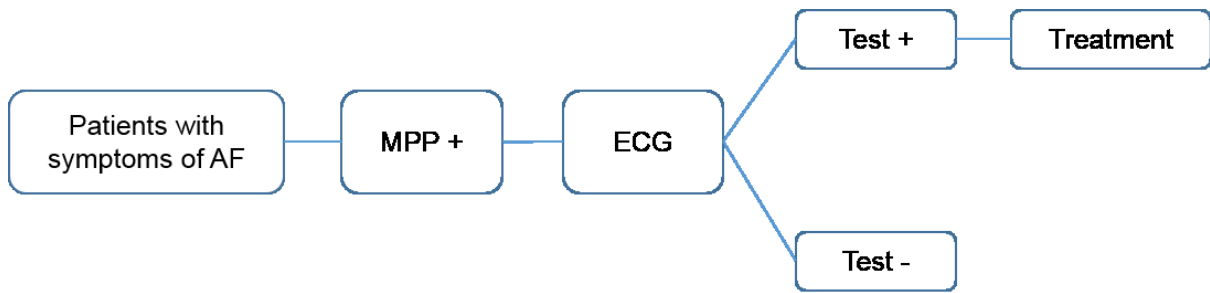
Figure 1 Current clinical pathway

AF=atrial fibrillation; ECG=electrocardiogram, MPP=manual pulse palpation

If shown to be a cost-effective option for the diagnosis of AF, lead-I ECG devices will be used in the diagnostic pathway for people with signs and symptoms of atrial fibrillation after manual pulse palpation has revealed an irregular pulse. Where atrial fibrillation is detected by a lead-I ECG, anticoagulation treatment would initially be started with a non-vitamin K antagonist therapy until further assessment has been done. A 12-lead ECG would subsequently be used to identify any additional abnormalities, such as left ventricular hypertrophy, which need to be considered when deciding on further treatment. A diagnosis of AF detected by a lead-I ECG and not subsequently detected by a 12-lead ECG may suggest paroxysmal AF. The alternative diagnostic pathway should lead-I ECG be found to be a cost-effective option is presented in Figure 2.
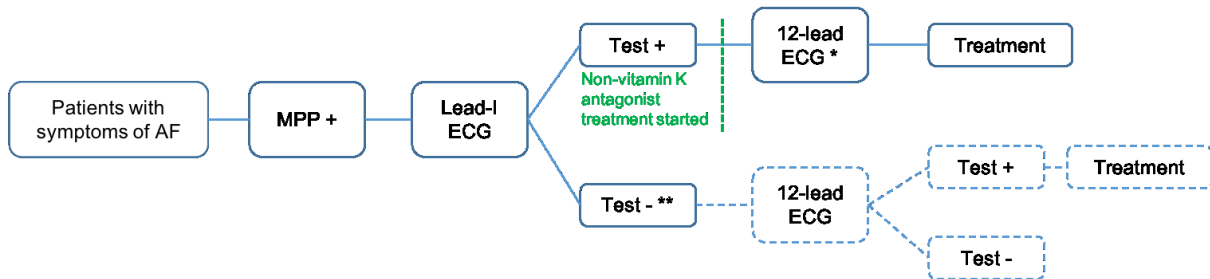
Figure 2 Proposed clinical pathway

* Not used for diagnosis of AF but to identify abnormalities that may need consideration to decide on further treatment
** Patients with a negative lead-I ECG after manual pulse palpation revealed an irregular pulse would have a subsequent 12-lead ECG if it is suspected that non-AF arrhythmia is causing the symptoms
AF=atrial fibrillation; ECG=electrocardiogram, MPP=manual pulse palpation

Management of atrial fibrillation

An overview of the treatment pathway described in CG180[2] is provided in Figure 3. As shown in Figure 3, the management of AF is subdivided into four algorithms.
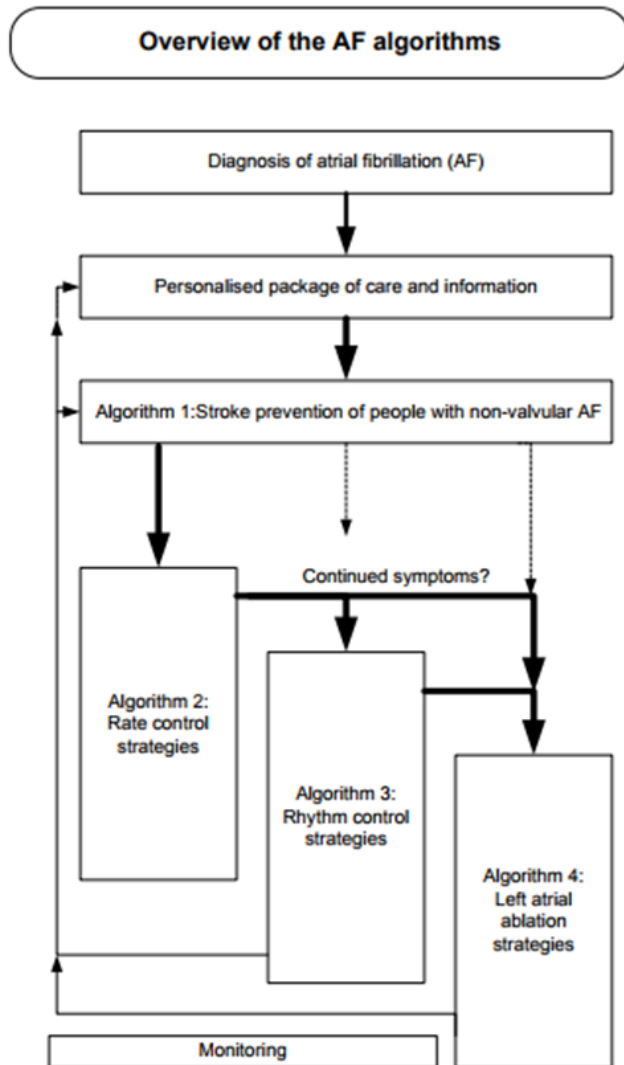
Figure 3 Overview of atrial fibrillation algorithms
Source: NICE CG180[2]

The aim of treatment is to reduce the symptoms of AF and prevent potential consequences of undiagnosed AF such as stroke.[2]

Reducing stroke risk

In CG180,[2] NICE recommends that patients with AF are assessed for their risk of stroke and risk of bleeding. The risk of stroke should be assessed using the CHA_2DS_2VASc[9] (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, female) algorithm and risk of bleeding should be assessed using the HAS-BLED[10] (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INR [international normalised ratio], elderly, drug/alcohol usage) algorithm.

Depending on the age of the patient, the results of the CHA_2DS_2VASc[9] assessment and the results of the HAS-BLED[10] assessment, patients with non-valvular AF may be offered stroke prevention treatment with either a vitamin K antagonist (usually warfarin) or newer oral anticoagulant (NOAC), either apixaban, dabigatran extilate, rivaroxaban or edoxaban.

Rate and rhythm control

In CG180,[2] NICE recommends (with some exceptions) that people with AF who need drug treatment as part of their rate control strategy should be offered either a standard beta-blocker or a rate-limiting calcium-channel blocker. Digoxin may be offered to sedentary people who have non-paroxysmal AF.

If monotherapy does not control the AF symptoms, and the symptoms are due to poor ventricular rate control, dual therapy with a beta-blocker, diltiazem or digoxin is recommended.

For rhythm control, NICE recommends pharmacological treatment with or without electrical rhythm control (cardioversion).

In CG180,[2] NICE also recommends strategies for left atrial ablation (left atrial ablation and pace and ablate) to control AF.

2.3 Comparator

To evaluate the clinical impact of lead-I ECG, the comparator of interest is manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy.

2.4 Interventions / index tests

The interventions / index tests to be assessed are lead-I ECG devices. Lead-I ECG devices are handheld instruments that can be used in primary care to detect AF at a single time point in people who present with relevant signs and symptoms. Lead-I ECG devices may also be used for ongoing or repeated testing for AF, which is outside of the scope of this assessment. Lead-I ECG devices feature touch electrodes, internal storage for ECG recordings, software with an algorithm to interpret the ECG trace and indicate the presence of AF. Data from the lead-I ECG devices can be uploaded to a computer to allow further analysis if necessary (e.g. in cases of paroxysmal AF).

The manufacturers of lead-I ECG devices all state that the diagnosis of AF should not be made using the algorithm alone and the ECG traces measured by the devices should be reviewed by a qualified healthcare professional. The use of lead-I ECG devices following detection of an irregular pulse by manual pulse palpation may allow people with AF to initiate and benefit from earlier treatment with anticoagulants.

Five different lead-I ECG devices are included in the NICE scope: imPulse,[11] Kardia Mobile,[12] MyDiagnostick,[13] RhythmPad GP[14] and Zenicor ECG.[15] The features of each device are described in turn in this section. All devices are CE marked.

2.4.1 imPulse (Plessey Semiconductors Ltd)

The imPulse (™) lead-I ECG device is provided with downloadable software for data analysis (imPulse Viewer) and a cable for charging the device. The ECG readings are taken by holding the device in both hands and placing each thumb on a separate sensor on the device for a pre-set length of time (from 30 seconds to 10 minutes). To operate, the device requires the associated software to be installed on a nearby PC or tablet. Data are transferred to hardware hosting the analytical software using Bluetooth, with the recorded ECG trace being displayed in real-time.

Once the recording has finished, the generated ECG trace can be saved in the imPulse viewer. Previously recorded readings can also be loaded into this viewer and ECG traces can be saved as a PDF. The software has an AF algorithm which analyses the reading and states whether AF is unlikely, possible or probable. In the event of a 'possible' or 'probable' result, the company recommends that the individual should undergo further investigation, and that the algorithm should not be used for a definitive clinical diagnosis of AF.

2.4.2 Kardia Mobile (AliveCor Ltd)

The Kardia Mobile lead-I ECG device works with the Kardia Mobile app to record and interpret ECGs. In addition to the Kardia Mobile device and app (which is free to download), a compatible Android or Apple smartphone or tablet is required.

Two fingers from each hand are placed on the Kardia Mobile device to record an ECG that is sent wirelessly to the device hosting the Kardia Mobile app. The default length of recording is 30 seconds, however this can be extended up to 5 minutes. The measured ECG trace is then automatically transmitted as an anonymous file to a European server for storage as an encrypted file.

The app uses an algorithm to classify measured ECG traces as either (i) normal, (ii) possible AF detected, or (iii) unclassified. The instructions for use state that the Kardia Mobile app assesses the patient for AF only, and the device will not detect other cardiac arrhythmias. Any detected non-AF arrhythmias, including sinus tachycardia, are labelled as unclassified. The company states that any ECG labelled as 'possible AF' or 'unclassified' should be reviewed by a cardiologist or trained healthcare professional. ECG traces measured by the device can be sent from a smartphone or tablet by email as a PDF attachment and stored in the patient's records. The first version of the Kardia app did not have automatic diagnostic functionality.

The atrial fibrillation algorithm was added to the app from January 2015. The Kardia Mobile has previously been available as the AliveCor Heart Monitor.

2.4.3 MyDiagnostick (Mydiagnostick Medical B.V.)

The MyDiagnostick is a handheld lead-I ECG device. An ECG recording is generated by holding metal handles at each end of the device, which act as electrodes for 1 minute. A light on the device will turn green if no AF is detected, or red if AF is detected. If an error occurs during the reading the device produces both an audible warning and a visible warning from the light on the device. Up to 140 ECG recordings can be recorded on the device before it starts to overwrite previous recordings. The MyDiagnostick device can be connected to a computer via a USB connection to download the generated ECG trace for review and storage using free software that can be downloaded from the MyDiagnostick website.

2.4.4 RhythmPad GP (Cardiocity)

The RhythmPad GP is a lead-I ECG device which is provided with software for data analysis. Lead-I ECG readings are taken by placing the palms of both hands on the surface of the device for 30 seconds after first being cleaned with an alcohol gel. Alternative configurations can be used if a person is unable to place their hands flat on the device, for example if they have arthritis. The software needs to be installed on a device running Windows XP or a later version and which has a USB port. Data are transferred directly to a computer using the USB connection for storage on the device's hard drive in PDF format.

The software includes an algorithm that can determine if a person is in AF, or has bradycardia, tachycardia, sinus arrhythmia, premature ventricular contractions or right bundle branch block. The recorded ECG trace is also available for further analysis by a healthcare professional. The company recommends that a 12-lead ECG is used to confirm a case of AF detected by the RhythmPad GP device.

2.4.5 Zenicor-ECG (Zenicor Medical Systems AB)

The Zenicor-ECG is a system with two components: a lead-I ECG device (Zenicor-EKG 2) and an online system for analysis and storage (Zenicor-EKG Backend System version 3.2). The online system is not locally installed, the device transmits data to a remote server which can be accessed using a web browser without prior installation of software, and requires a user licence. ECG readings are taken by placing both thumbs on the device for 30 seconds. The instructions for use state that the electrodes in the Zenicor EKG-2 should be replaced after every 500 measurements. The device is powered by three alkaline batteries that the company states are expected to last for at least 200 measurements and transmissions.

Once a measurement is made using the Zenicor-EKG 2 device, the ECG measurement can be transferred from the device (using a built-in mobile network modem) to a Zenicor server in Sweden. Here the ECG is analysed using the Zenicor-EKG Backend System, which includes an automated algorithm. This can categorise an ECG into one of 12 groups corresponding to potential arrhythmias; 1 of which includes AF. The algorithm will also report if the recorded ECG cannot be analysed. The company states that a clinician needs to manually interpret the ECG trace generated by the Zenicor-ECG to make a final diagnosis of AF.

The measured ECG trace can be downloaded or printed as a PDF report. The company states that the ECG is available via the web-interface about 4 to 5 seconds after the ECG has been transmitted from the device.

The company states that the Zenicor EKG-2 does not store, contain or transmit any patient identifiable information. ECGs are sent via the built-in mobile network modem to the Zenicor server labelled with the device's identity number. Communication between the Zenicor server and a web browser accessing it are encrypted.

2.5   Reference standard

The index test will be compared to the results of a reference standard for the purposes of assessment of diagnostic accuracy. The reference standard is used to verify the presence or absence of the target condition. The reference standard for this assessment is a 12-lead ECG performed and interpreted by a trained healthcare professional.

3 METHODS FOR ASSESSING CLINICAL EFFECTIVENESS AND DIAGNOSTIC TEST ACCURACY

A systematic literature review will be conducted to evaluate the clinical impact of single-time point lead-I ECG devices relative to manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy, and the diagnostic accuracy of single-time point lead-I ECG for the diagnosis of AF using 12-lead ECG as the reference standard. The systematic review methods will follow the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care,[16] NICE's Diagnostics Assessment Programme manual[17] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[18]

3.1 Eligibility criteria

The eligibility criteria required for studies to be included in the review of the clinical effectiveness evidence are presented in Table 2.

Although the index test (i.e. interventions being evaluated) must have been performed in a primary care setting, studies in which the index tests are interpreted by a cardiologist will be eligible because it is plausible that the test results could be sent for remote interpretation by a cardiologist.

Studies not presenting original data (i.e. reviews, editorials and opinion papers), case reports and non-English language studies will be excluded from the review. Conference proceedings published from 2013 onwards will be screened.

Table 2 Inclusion criteria

Population	People with signs or symptoms that may indicate underlying AF and who have an irregular pulse	
Setting	Primary care	
Interventions / index tests	Lead-I ECG using one of the following technologies: • imPulse • Kardia Mobile • MyDiagnostick • RhythmPad GP • Zenicor-ECG	
	Clinical impact	**Diagnostic test accuracy**
Comparator	Manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy or other lead-I ECG devices as specified above	Other lead-I ECG devices as specified above, or no comparator
Reference standard	Not applicable	12-lead ECG performed and interpreted by a trained healthcare professional
Outcomes	Intermediate outcomes • Time to diagnosis of AF • Time to initiation of preventative treatment (such as interventions to prevent stroke) • Concordance between lead-I ECG devices • Test failure rate • Time to complete testing and store produced ECG trace • Ease of use of devices (for patients and healthcare professionals), including training requirements • Impact of test results on clinical decision making • Number of 12-lead ECGs carried out • Diagnostic yield (number of AF diagnoses)	Diagnostic accuracy • The numbers of true positive, false negative, false positive and true negative test results
	Clinical outcomes • Mortality • Morbidity (including stroke, other thromboembolisms and heart failure, and any complications arising from preventative treatments, such as adverse effects of anti-arrhythmic, rate control or anticoagulation treatment)	
	Patient-reported outcomes • Health-related quality of life • Acceptability of the devices	
Study design	RCTs, cross-sectional, case-control, cohort studies and uncontrolled single arm studies. Qualitative studies will be considered to evaluate the ease of use of the devices	Diagnostic cross-sectional and case-control studies

AF=atrial fibrillation; ECG=electrocardiogram; RCT=randomised controlled trial

3.2 Search strategy

The search strategies will be designed to focus on the specified devices (i.e. imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor ECG) and target condition (i.e. AF) as recommended in the CRD guidance for undertaking reviews in health care[16], NICE's Diagnostics Assessment Programme manual[17] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[18] No study design filters will be applied and all electronic databases will be searched from inception until the latest available version. The reference lists of relevant systematic reviews and eligible studies will be hand-searched to identify further potentially relevant studies. Data submitted by the companies/sponsors will be considered (please see Section 5.1 for further details).

The following databases will be searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print and MEDLINE In-Process (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane)
- Cochrane Central Database of Controlled Trials (CENTRAL) (Cochrane)
- Database of Abstracts of Reviews of Effects (DARE) (Cochrane)
- Health Technology Assessment Database (HTA) (Cochrane)

Details of the draft MEDLINE search strategy can be found in Appendix 1. The MEDLINE search will be adapted to enable similar searching of the other relevant electronic databases.

3.3 Study selection

The citations identified will be assessed for inclusion through two stages. First, two reviewers will independently screen all the titles and abstracts identified by the searches of electronic databases to identify the potentially relevant articles to be retrieved. Full-text copies of the selected studies will subsequently be obtained and assessed independently by two reviewers for inclusion using the eligibility criteria outlined in Table 2. Any disagreements will be resolved by discussion at each stage, and, if necessary, a third reviewer will be consulted.

3.4 Data extraction

A data extraction form will be developed and piloted for the purposes of this assessment. The data extracted will include information on study authors and year of publication, study design, characteristics of study participants, prevalence of comorbidities, prevalence of AF by type, characteristics of the index tests (including length of monitoring, who performed and interpreted the results), characteristics of the reference test (including length of monitoring, who performed and interpreted the results), the order in which the index test and comparator were performed, whether the person who interpreted the reference standard test was blind to

the results of the index test, and the outcome measures as described in Table 2. Data will be extracted from eligible studies by one reviewer and checked for accuracy by a second reviewer. Any disagreements will be resolved by discussion, and, if necessary, a third reviewer will be consulted. If time permits, authors (and sponsors) of the studies will be contacted for missing data.

3.5 Quality assessment

The methodological quality of included diagnostic accuracy studies will be assessed using the QUality Assessment of Diagnostic Accuracy Studies - 2 (QUADAS-2) tool tailored to the review question.[19] The QUADAS-2 tool considers four domains: patient selection, index test(s), reference standard and flow of patients through the study and timing of the tests. If any randomised controlled trials (RCTs) evaluating the clinical impact of lead-I ECGs are identified, these studies will be assessed using the Cochrane Risk of Bias tool.[20] Non-randomised studies will be assessed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions).[21] If sufficient data are available, the results of the quality assessment exercise may be used to inform sensitivity analyses to explore the impact of the different domains of study quality upon the findings of the review. Qualitative studies will be assessed using the Critical Appraisal Skills Programme (CASP) tool.[22] Quality assessment of the included studies will be undertaken by one reviewer and checked for accuracy by a second reviewer. Any disagreements will be resolved by discussion, and, if necessary, a third reviewer will be consulted.

3.6 Methods of analysis/synthesis of diagnostic accuracy studies

3.6.1 Statistical analysis and data synthesis

<u>Individual study results</u>

The sensitivity and specificity of each index test from individual studies of diagnostic accuracy will be summarised on forest plots and plotted in receiver operating characteristic (ROC) space.

<u>Meta-analysis</u>

If meta-analysis is appropriate given the number of studies and extent of clinical heterogeneity, we will use the bivariate model to obtain pooled estimates of sensitivity and specificity.[23] The bivariate model will be used to compare the accuracy of lead-I ECG devices with 12-lead ECG by adding a covariate for test type to the model. Data permitting, in additional analyses, we will compare the accuracy of different lead-I ECG devices by adding a covariate for device type to a bivariate meta-analysis of lead-I ECG. The bivariate model will be fitted using the

meqrlogit command in Stata version 14. If meta-analyses are not possible, the results of the included studies will be synthesised narratively.

3.6.2   Subgroup analyses

If data are available, the EAG will assess the impact of the following variables on the accuracy of lead-I ECG devices by performing subgroup analyses or meta-regression (by inclusion as a covariate in a bivariate model):

- Type of AF
- Setting where reference standard is performed (i.e. primary or secondary care)
- Use of the device's algorithm alone or interpretation of the lead-I ECG trace
- People who are unable to use the device electrodes as recommended by the companies (for example, people with movement disorders).

3.6.3   Sensitivity analyses

If data are available, the EAG will conduct sensitivity analyses by excluding studies judged to have a high risk of bias, or if the EAG is uncertain about the appropriateness of including them in the primary meta-analyses.

3.7   Methods of analysis/synthesis of clinical impact studies

If meta-analysis of the clinical and intermediate outcomes stated in Table 2 is possible, we will use fixed effect or random effects models to pool effect measures as appropriate. Statistical heterogeneity will be assessed using chi-square and I^2 statistics. Depending on the level of clinical and statistical heterogeneity, subgroup and sensitivity analyses will be explored.

3.8   Other considerations

Studies that assess the accuracy of lead-I ECG devices used at a single-time point to detect atrial fibrillation in an asymptomatic population will be considered for inclusion if there is a lack of studies in symptomatic populations.

The inclusion of uncontrolled single arm studies may be restricted by number of patients' recruited following consideration of the data derived from comparative studies.

'Real world' data on the use of lead-I devices will be included in the assessment if possible to be obtained in sufficient detail to be critically appraised and applicable to the decision problem.

4 METHODS FOR ASSESSING COST EFFECTIVENESS

The economic evaluation will assess the cost effectiveness of single-time point lead-I ECG devices compared with manual pulse palpation followed by a 12-lead ECG in primary or secondary care (prior to initiation of anticoagulation therapy) in people presenting to primary care with signs and symptoms of AF who have an irregular pulse. The economic evaluation will include a review of existing economic evaluations of lead-I ECG devices and the creation of a de novo economic model.

4.1 Identifying and systematically reviewing published cost-effectiveness studies

A systematic review will be undertaken to identify published full economic evaluations of lead-I ECG devices for detecting AF. A search filter to identify economic evaluations will be applied to the search strategies and the electronic databases will be searched from inception until the latest available version.

The following databases will be searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print and MEDLINE In-Process (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane)
- Cochrane Central Database of Controlled Trials (CENTRAL) (Cochrane)
- Database of Abstracts of Reviews of Effects (DARE) (Cochrane)
- Health Technology Assessment Database (HTA) (Cochrane)
- EconLit (EBSCO)
- NHS Economic Evaluation Database (NHS EED)

Broader searches will be carried out to identify existing economic models of AF and ECG. Separate searches will be carried out for supporting information on costs and health state utility data. Study selection and data extraction will be carried out as described in Sections 3.3 and 3.4 respectively. The methodological quality of the full economic evaluations identified in the review will be assessed using the Drummond checklist.[24]

A narrative synthesis and structured tables will be used to present the main findings from the economic evaluations identified via the systematic review.

4.2 Development of a health economic model

An economic model will be developed following the completion of the systematic review and discussion with clinical experts. The model will be used to assess the cost effectiveness of alternative lead-I ECG devices (imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor-ECG) in comparison to manual pulse palpation followed by a 12-lead ECG in primary

or secondary care (prior to initiation of anticoagulation therapy) for detecting AF in people presenting to primary care with signs and symptoms of AF who have an irregular pulse.

Clinical effectiveness and diagnostic accuracy estimates will be taken from the results of the systematic review described in section 3. Other model parameters (e.g. utilities, cost data) will be populated from the results of the focused economic searches and from routine sources (e.g. NHS reference costs).[25] The EAG will elicit expert opinion if published data are not available for some model parameters. All evidence will be evaluated according to the recommendations of the NICE Diagnostics Assessment Programme manual.[17]

4.2.1 Model structure

The model will be structured taking into consideration previous economic models in the area of ECG and cardiovascular disease. It is anticipated that the event pathways will be modelled by a decision tree to estimate short-term outcomes including results of the diagnostic tests, followed by a Markov cohort structure to model long-term costs and benefits. The economic model will incorporate the pathways of care that individuals follow under standard practice in the UK NHS and for which credible evidence is available. The EAG will review previous economic models and seek expert clinical advice to help structure the diagnostic and care pathways. Therefore, the model structure described here might change, as the final structure will be dependent on the findings from the literature reviews and consultation with clinical experts. It is expected that a linked-evidence modelling approach may be required, as the results of initial scoping searches indicate that studies assessing lead-I ECGs often focus on diagnostic accuracy rather than on long-term clinical outcomes resulting from the use of these devices.

The patient population considered in the model will be people presenting to primary care with signs and symptoms of AF and an irregular pulse. The economic assessment will be undertaken from the perspective of the NHS and Personal Social Services. The model time horizon will be set to patient lifetime (estimated to be 30 years in the base case) and both costs and benefits will be discounted at 3.5% per annum.

The NICE guideline on AF[2] recommends that manual pulse palpation should be used to assess for the presence of an irregular pulse, followed by an ECG in people with signs and symptoms of AF who have an irregular pulse (see Figure 1). Lead-I ECG devices would be used in the diagnostic pathway for people with signs and symptoms of atrial fibrillation after manual pulse palpation has revealed an irregular pulse (see Figure 2). If judged appropriate, the EAG will incorporate scenarios into the economic model to evaluate different diagnostic pathways using the lead-I ECG devices.

Model results will be presented as incremental cost per quality adjusted life year (QALY) ratios. Appropriate sensitivity analyses will be undertaken to assess the robustness of the model results to realistic variations in the underlying data. Where the overall results are sensitive to a particular variable, the sensitivity analysis will analyse the exact nature of the impact of variations. Imprecision in the principal model's cost effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question (e.g. multi-way sensitivity analysis, probabilistic sensitivity analysis, cost effectiveness acceptability curves).

5 OTHER INFORMATION

5.1 Handling information from the companies

Data submitted by the manufacturers/sponsors will only be considered if received by the EAG no later than 29/05/2018. Data arriving after this date will not be considered. Any data that meet the inclusion criteria stated will be extracted and quality assessed as stated in the methods section of this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. All confidential data used in the cost effectiveness models will also be highlighted.

5.2 Competing interests of authors

None of the authors have any competing interests.

5.3 Project timetable/milestones

Milestones	Date to be completed
Draft protocol	31st January 2018
Final protocol	23rd February 2018
Progress report	29th May 2018
Draft assessment report	24th July 2018
Final assessment report	21st August 2018

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7 APPENDICES

7.1 Appendix 1 Draft search strategy (MEDLINE)

1   Lead-I ECG.tw.

2   single lead ECG.tw.

3   (lead I or single lead or automated algorithm).tw.

4   Electrocardiography/

5   (electrocardiog* or ECG).tw.

6   4 or 5

7   3 and 6

8   lead I electrocardiog*.tw.

9   single lead electrocardiog*.tw.

10   1 or 2 or 7 or 8 or 9

11   Atrial Fibrillation/

12   AF.tw.

13   (Atr* adj3 Fibrill*).tw.

14   11 or 12 or 13

15   10 and 14

16   Kardia Mobile.tw.

17   MyDiagnostick.tw.

18   RhythmPad.tw.

19   Zenicor-ECG.tw.

20   imPulse.tw.

21   10 and 20

22   15 or 16 or 17 or 18 or 19 or 21

23   Animals/ not Humans/

24   22 not 23