Early Value Assessment commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Final Protocol

Title of project

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication: A systematic review to inform Early Value Assessment (EVA)

Name of External Assessment Group (EAG) and project lead

Kleijnen Systematic Reviews Ltd. Assessment Group

Project lead: Marie Westwood
Second Contact: Nigel Armstrong
Kleijnen Systematic Reviews Ltd
[redacted]
Tel: [redacted]
Email: [redacted]

Health economics lead: Isaac Corro Ramos
Second contact: Maiwenn Al
Institute for Medical Technology Assessment/Institute of Health Policy and Management
Erasmus University
[redacted]
Tel: [redacted]
Email: [redacted]

Plain English Summary

Some medicines used for people with certain mental health problems can increase the risk of developing serious heart conditions. Although these heart conditions are rare it is generally recommended that people have an electrocardiogram (ECG) examination before starting to take these medicines. People who need to continue on these medications over a period of time may need additional ECGs every so often, to check for any heart problems that have developed recently.

An ECG is a test to check whether there are any problems with the heartbeat. This can include a heartbeat that is irregular or too fast. ECGs are usually carried out in hospitals or GP surgeries. The machine that is most often used is called a 12-lead ECG. A nurse or doctor will ask the patient to remove their upper clothing and it is possible that the patient's skin might need to be cleaned or shaved. The nurse or doctor will then place several small electrodes onto different parts of the patient's body including the chest, wrists and ankles. A special gel is applied underneath the electrodes to help them pick up the heartbeat. This gel usually feels cold on the skin. The patient is asked to keep still for a few minutes while the ECG test is being done. The ECG records a tracing of the heartbeat from different angles which can help to show which part of the heart has a problem. The ECG tracing can be viewed on a screen or saved as an electronic file or printed on paper. Having an ECG is not painful and does not involve delivering an electric shock to the patient. However, some people may find the procedure upsetting because having to undress and be washed or shaved or having a cold gel applied may be distressing or unacceptably intrusive. In addition, some patients may have difficulty in travelling to a hospital or GP surgery to have the ECG carried out.

KardiaMobile 6L is a portable (or 6-lead) ECG may offer a less intrusive way to take ECG measurements. This is because less undressing is not needed since the electrodes are only applied to the wrists and ankles and the cold gel is not needed. Testing using the KardiaMobile 6L device can be carried out at the patient's home. These features might mean that the KardiaMobile 6L device could be more acceptable than the 12-lead ECG to some patients.

This assessment will consider whether the KardiaMobile 6L device has the potential to provide an effective and safe alternative to 12-lead ECG for initial assessment and monitoring of the risk of cardiac problems in people taking antipsychotic medications.

1 Decision problem

1.1 Population

The primary indication for this assessment is the use of the KardiaMobile 6L, 6-lead ECG device for the assessment of QT-interval-based cardiac risk in service users prior to the initiation of antipsychotic medications, which are associated with an established risk of QT interval prolongation, and for monitoring QT-interval-based cardiac risk once medication has been established. NICE clinical guidelines CG178 and CG185 on the prevention and management of psychosis and schizophrenia in adults[1] and the assessment and management of bipolar disorder[2] recommend that a person should be offered an ECG before starting antipsychotic medication if:

- specified in the drug's summary of product characteristics
- a physical examination has identified specific cardiovascular risk
- there is a family history of cardiovascular disease, sudden collapse, or other cardiovascular risk factors such as arrhythmia
- the service user is being admitted as an inpatient

A guideline from the NHS Northern England clinical network[3] states that a baseline ECG should be done for all people starting antipsychotic medication. Published recommendations, from Leeds Teaching Hospitals NHS Trust,[4] provide an algorithm for what clinicians should do when considering prescribing QT-prolonging medication. This algorithm includes the recommendations for the use of baseline and monitoring ECG, suggesting that when initiating drugs with a high risk of QTc prolongation, ECG should be done at baseline, and may be repeated once the drug reaches therapeutic levels (4-5 half-lives).[4] If the service user is taking other QTc prolonging medication, or has risk factors for QT interval prolongation, then regular ECG monitoring is recommended. ECG is also recommended after dose changes.[4] The British Heart Rhythm Society clinical practice guidelines on the management of patients developing QT prolongation on antipsychotic medication recommend that QT interval is measured using either lead-II or V5.[5]

This assessment will consider the potential clinical effectiveness of using KardiaMobile 6L for the initial assessment (triage) of QT-interval-based cardiac risk in service users prior to the initiation of antipsychotic medications, which are associated with an established risk of QT interval prolongation, and for monitoring QT-interval-based cardiac risk once medication has been established. The assessment of KardiaMobile 6L as a triage step means that patients with QT prolongation, identified by KardiaMobile 6L, would be followed up using 12-lead ECG. There may be additional circumstances where follow-up 12-lead ECG is required, e.g. where the KardiaMobile 6L readout is considered to be of insufficient quality for clinical decision making.

1.2 Presentations for which antipsychotic medications, associated with a risk of QT prolongation, may be prescribed

Psychosis and schizophrenia

Psychosis (sometimes referred to as psychotic episodes or experiences) is a mental health condition that causes people to see or interpret things differently to other people. The main manifestations of psychosis are hallucinations and delusions. Psychotic disorders, based on the WHO International Classification of Diseases chapter on Mental and Behavioural Disorders Diagnostic Criteria for Research (ICD-10),[6] comprise two main types: schizophrenia and affective psychosis. Antipsychotic medications may be variously given, in service users with these conditions, to treat acute episodes and/or as part of long-term management.[1] The NHS Digital, Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014[7] reported the overall prevalence of psychotic disorders as 0.4% in 2007 and 0.7% in 2014[7] and noted that were no significant differences in rate between men and women. This survey used interviews with a sample of the household population, 7,500 people aged 16 or over, including those who do not access services.[7] Although the observed rate was highest in those aged 35–44, associations with age were not statistically significant for the year 2014.[7] However, psychotic disorders were associated with ethnic group with rates found to be higher in black men (3.2%) than men from other ethnic groups; rates of psychotic disorder did not vary significantly between ethnic groups among women.[7] Socioeconomic factors were also reported to be strongly linked with psychotic disorder, with psychotic disorder being more common in those who are economically inactive.[7] Overall, four-fifths of people identified with psychotic disorder were reported to be in receipt of treatment, and approximately 76% were currently taking psychotropic medications.[7]

Bipolar disorder

Bipolar disorder is a mental health condition in which a person experiences episodes of mania and episodes of depressed mood which can last for several weeks or months.[2] The peak age of onset is 15–25 years, and there is often a substantial delay between onset and first contact with mental health services.[2] Approximately 1 in every 50 adults will have bipolar disorder at some point in their life.[2] The NHS Digital, Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014[7] used a 15-item Mood Disorder Questionnaire to screen for bipolar disorder, with a positive screen requiring endorsement of at least 7 lifetime manic/hypomanic symptoms, as well as several co-occurring symptoms, together with moderate or serious functional impairment; a positive screen indicated the likely presence of bipolar disorder and that fuller assessment would be warranted. Overall, 2.0% of the NHS Digital, Mental Health and Wellbeing in England population screened positive for bipolar disorder; rates were similar in men and women and a positive screen was more common in younger age groups (3.4% of 16-24 year olds) and in economically inactive participants.[7] Approximately 39% of those screening positive for bipolar disorder were currently receiving some form of psychotropic medication.[7]

Treatment-resistant depression

Based on the NICE definition of people with treatment-resistant depression, as those who have not responded to two antidepressants,[8] approximately 2.7 million people in the UK have treatment resistant depression (between 10% and 30% of people with depression). [9] If a person has depression that does not respond well to initial treatment with antidepressants, concomitant antipsychotic medication such as aripiprazole, olanzapine, quetiapine or risperidone may be used to augment treatment.[9] Decisions to use antipsychotics in this manner should be made with care given that some antidepressants can also prolong the QT interval.[9]

Dementia

People with dementia may experience severe agitation, aggression or psychotic symptoms. According to the NICE guideline on dementia:[10] assessment, management and support for people living with dementia and their carers, antipsychotic medications may be offered for people with these symptoms if they are at risk of harming themselves or others, or if they are experiencing agitation, hallucinations or delusions that are causing them severe distress. Apart from risperidone and haloperidol, this is generally an off-label use of antipsychotics.[11] NICE also recommends conducting a structured assessment to explore possible reasons for the distress before considering antipsychotic medication. It is recommended to use the lowest effective dose for the shortest possible time, and to reassess the person at least every 6 weeks to check whether ongoing medication is still required.

This assessment will provide a comprehensive summary of the evidence about the performance of KardiaMobile 6L as a triage test for the assessment of QT-interval-based cardiac risk in service users prior to the initiation of antipsychotic medications, which are associated with an established risk of QT interval prolongation, and for monitoring QT-interval-based cardiac risk once medication has been established. The assessment will consider whether the KardiaMobile 6L device has the potential to provide an effective and safe alternative to 12-lead ECG for initial assessment and monitoring of the risk of cardiac problems in people taking antipsychotic medications and will include a detailed description of evidence gaps where further research is required. This assessment will not include cost effectiveness modelling, but may inform exploratory modelling to be undertaken by the NICE Decision Support Unit (DSU).

1.3 Intervention technologies

People taking antipsychotic medications, which are associated with an established risk of QT interval prolongation, may need to be screened for QT prolongation before initiation of treatment and monitored for the development of QT prolongation if treatment is ongoing.

Current practice is to use 12-lead ECG devices in primary or secondary care centres. An ECG is a test to measure heart rhythm and electrical activity. Electrodes in contact with the skin

detect the electrical signals produced by the heart as it beats. Multiple views of the heart can be recorded by placing electrodes at different places on the body. These different views are referred to as ECG leads and are displayed as separate traces on the output.[12] A conventional ECG records 12 leads using 10 electrodes, which are split into 6 limb leads which view the heart in a vertical plane, and 6 precordial leads which view the heart in a horizontal plane

Twelve-Lead ECG devices require the service user to partially undress and the healthcare practitioner needs to use conductive gel to create contact between the service user's skin and the electrodes. Some people may find these requirements distressing or unacceptably intrusive. Some portable ECG devices offer a less intrusive way to take ECG measurements that require less undressing (limb only electrodes) and may eliminate the need for conductive gel and may therefore be more acceptable to patients.

Some people needing ECG assessments may find travel or attendance at healthcare centres for appointments difficult. Portable ECG devices are easily transported so can be used by community healthcare practitioners in home visits. Use of the devices could increase the likelihood that people will have an ECG done regularly and may result in more cardiac irregularities being identified. Additionally, these devices have the potential to reduce costs and time associated with ECG monitoring by reducing the number of appointments in hospitals or GP surgeries and could release capacity for 12- lead ECG use for other indications.

KardiaMobile 6L (AliveCor)

The KardiaMobile 6L is a portable 6-lead ECG device that is manufactured by AliveCor. It uses 3 electrodes to record a person's ECG and wirelessly transmits the data as a PDF to a compatible smartphone or tablet via Bluetooth. This can then be sent via email to physicians. User data are stored on a GDPR-compliant cloud-based system hosted in Frankfurt, Germany. The device is powered by a single coin cell battery.

There are 2 electrodes on the top of the device for use with the left and right hands, and 1 on the bottom of the device for use with the bare skin of the left knee or inside of ankle. The service user is usually seated for the test. In single-channel mode, the KardiaMobile 6L can record Lead-I ECG. In 2- channel mode, it can record a 6-lead ECG.

The company has stated that healthcare professionals can be trained quickly by following the instructions for use and instructions from within the app, but training by company representatives can be supplied if required.

The company have further stated that the device provides an instant algorithmic analysis of a person's heart rhythm upon completion of the ECG recording. This indicates normal sinus rhythm, atrial fibrillation, bradycardia, tachycardia, or an unclassified result for both single-

lead and 6-lead ECGs. Currently, QT interval must be calculated by the user, however the company is developing software to allow automated QT interval analysis.

In a pilot programme, the results of the test were shared with a cardiologist or other appropriate clinician for analysis, and then sent to the service user's clinical team with any abnormalities highlighted.[13] A 12-lead ECG may be required in cases where the outcome of the 6-lead device is unclear, or if other heart conditions such as ischaemia or left ventricular hypertrophy are suspected.[14]

The KardiaMobile 6L has not been tested for and is not intended for paediatric use. The company state that significant body fat, body hair or very dry skin can interfere with the electrodes. Exposure to strong magnetic fields, for example from a cardiac pacemaker or implantable defibrillator, can also cause interference.

1.4 Target condition(s)

Some antipsychotic medications are associated with prolonged ventricular repolarisation, potentially giving rise to QT interval prolongation and subsequent arrhythmias, such as polymorphic ventricular tachycardia. This can cause convulsions, dizziness and fainting, and in rare cases can lead to ventricular fibrillation and sudden cardiac death.[15]

The target condition, with respect to assessing the accuracy of KardiaMobile 6L, is QT prolongation. Definitions of abnormal QTc vary. According to the NHS Northern England guideline,[3] a QTc is considered normal if below 440 milliseconds (ms) for men, or below 470 ms for women. ECG should be repeated annually if a normal QTc is detected. If an abnormal QTc of more than 500 ms is detected, the guideline recommends immediate cessation of the suspected drug and urgent referral to a cardiologist. If the abnormal QTc is less than 500 ms, it is advised to decrease the dose of antipsychotic or consider switching to an alternative drug with a lower risk of increased QTc. Dorset Medicines Advisory Group guidance for mental health prescribers[16] advises not to use QT-prolonging drugs if QTc is more than 460 ms and the patient has had an unexplained syncopal episode. If the QTc is between 480 and 499 ms, it is advised to consider alternative therapy or monitor QT interval monthly, to correct electrolyte imbalances, and to consider referral to cardiology. If the QTc is more than 500 ms or has increased by more than 60 ms, the QT-prolonging drug should be discontinued and the service user referred to cardiology. Khatib et al.[4] recommend that, if a significant change in QTc is observed (increase greater than 50 ms or absolute value more than 500 ms), dose reduction or drug cessation should be considered. Although cardiologists may be consulted in the case of uncertain ECGs, the authors note that the decision on dose change lies with the prescriber. This assessment will consider any reported definition of abnormal QTc.

QTc prolongation is, however, an interim outcome. This assessment will also consider the effects of implementing KardiaMobile 6L on the rates of adverse clinical outcomes, both cardiac and psychiatric.

1.5 Care pathway

Risk assessment

The National Clinical Audit of Psychosis recommended that people with psychotic disorders are assessed for risk of cardiovascular disease at least annually, using the Q-Risk tool.[17] The choice of antipsychotic medication, the starting dose and/or the increase in frequency of monitoring should then be influenced by the presence of any cardiovascular disease history, as well as other factors such as poor nutrition or liver disease.[15] Identification of any cardiovascular risk factors should also prompt a more detailed cardiac assessment including an ECG, which should be examined for evidence of ischaemic heart disease, left ventricular hypertrophy and repolarisation abnormalities.

It should be noted that assessments of general cardiac health fall outside the scope of this assessment; this assessment will focus on the use of ECG to assess QT-interval-based cardiac risk.

Treatment

During scoping discussions, clinical experts advised that changes to antipsychotic medication following detection of prolonged QT intervals are made following an assessment of the relative risk and benefit of treating the psychiatric condition versus cardiac side effects. The frequency of ECG monitoring may also be increased. Some experts noted that the risk of cardiac complications is often considered lower than the risks of psychotic symptoms if antipsychotics are not given.

This assessment will systematically review the evidence about the accuracy of KardiaMobile 6L, as an initial testing (triage) method for the detection of QT prolongation, in service users prior to the initiation of antipsychotic medications, which are associated with an established risk of QT interval prolongation, and for monitoring QT-interval-based cardiac risk once medication has been established. QTc prolongation is an interim outcome and this assessment will, therefore, systematically review evidence about effects of implementing KardiaMobile 6L on the rates of adverse clinical outcomes, both cardiac and psychiatric.

This assessment will also consider any reported information on testing up-take and acceptability or patient satisfaction outcomes, and other intermediate outcomes (e.g. ease of use, number of 12-lead ECG requests, number of cardiology referrals/requests for cardiology interpretation, test failure rates, change to clinical decision, time to antipsychotic use) reported in studies of relevant populations.

This assessment aims to provide a comprehensive summary of all available evidence that may be relevant to the potential implementation of KardiaMobile 6L, in the context of QT-interval assessment for service users who require antipsychotic medication. It is anticipated that currently available evidence will not be sufficient to inform assessment of the efficacy and safety of KardiaMobile 6L, in people taking antipsychotic medications, and to support full cost effectiveness modelling. The assessment will, therefore, focus on whether the KardiaMobile 6L device has the potential to offer advantages over the use of 12-lead ECG for initial assessment and monitoring of the risk of cardiac problems in people taking antipsychotic medications, such that further research to establish clinical efficacy and safety is warranted. The assessment will include a detailed description of evidence gaps where further research is required. This assessment will not include cost effectiveness modelling, but may inform exploratory modelling to be undertaken by the NICE Decision Support Unit (DSU).

2 Objectives

The overall aim of this project is to provide a comprehensive summary of all available evidence that may be relevant to the potential implementation of KardiaMobile 6L, in the context of QT-interval assessment for service users who require antipsychotic medication.

The assessment of KardiaMobile 6L as a triage step means that patients with QT prolongation, identified by KardiaMobile 6L, would be followed up using 12-lead ECG. Full cost effectiveness analysis should, therefore, compare KardiaMobile 6L, followed by 12-lead ECG in patients in whom QT prolongation is identified to 12-lead ECG in all patients (i.e. no triage step), or no ECG (in situations where 12-lead ECG is not available or is refused).

We have defined a series of research questions that would need to be addressed, to support a full assessment of the clinical- and cost-effectiveness of using KardiaMobile 6L for the initial assessment (triage) of QT-interval-based cardiac risk in service users prior to the initiation of antipsychotic medications which are associated with an established risk of QT interval prolongation, and for monitoring QT-interval-based cardiac risk once medication has been established:

- What are the clinical effects (on cardiac and psychiatric outcomes) of using KardiaMobile 6L for the initial assessment (triage) of QT-interval-based cardiac risk in service users taking antipsychotic medications that are associated with QT prolongation, both for baseline assessment before initiating medication and for ongoing monitoring, compared to 12-lead ECG in all patients (no triage step) or no ECG?

- What is the accuracy/technical performance of KardiaMobile 6L, where abnormal QTc interval, determined by 12-lead ECG (the reference standard method) is the target condition?

- What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?

- What are the costs, from a UK NHS and Personal Social Services perspective, of using KardiaMobile 6L for the initial assessment (triage) of QT-interval-based cardiac risk in service users taking antipsychotic medications that are associated with QT prolongation?

- What existing, published cost-effectiveness studies are available about QT-interval assessment for service users who require antipsychotic medication?

Given the anticipated limitations of the evidence base, this assessment will use a broader scope to consider whether the KardiaMobile 6L device has the potential to provide an effective and safe alternative to 12-lead ECG for initial assessment and monitoring of the risk of cardiac problems in people taking antipsychotic medications. The assessment will include evidence about secondary outcomes, which are not sufficient to inform decision making about routine use in UK NHS clinical practice, in the absence of higher-level outcomes data (evidence about the clinical efficacy and safety of the device). These outcomes will be included to inform consideration of the potential benefits of implementing the KardiaMobile 6L device, as specified in the scope, and hence to indicate whether further research to establish clinical efficacy and safety is warranted. The available evidence will be summarised, with consideration of its relevance to the above research questions, and a detailed description of evidence gaps where further research is needed will be provided. This assessment will not include cost effectiveness modelling, but may inform exploratory modelling to be undertaken by the NICE Decision Support Unit (DSU).

3 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[18] the NICE guide to methods of technology appraisal,[19] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[20]

3.1 Inclusion criteria

Separate inclusion criteria were developed for each of the clinical-effectiveness questions. These are summarised in Table 1.

Table 1: Inclusion criteria

Question	What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QT prolongation, determined by standard 12-lead ECG (the reference standard method)?	What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?	What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?	What are the costs, from a UK NHS and Personal Social Services perspective, of using KardiaMobile 6L for the initial assessment (triage) of QT-interval-based cardiac risk in service users taking antipsychotic medications that are associated with QT prolongation?[a]	What existing, published cost-effectiveness studies are available about QT-interval assessment for service users who require antipsychotic medication?
Participants:	Any population[b]	People starting or maintained on antipsychotic medications that are associated with QT prolongation, in whom an ECG assessment of QT-based cardiac risk is indicated	People starting or maintained on antipsychotic medications that are associated with QT prolongation, in whom an ECG assessment of QT-based cardiac risk is indicated (service user acceptability/satisfaction) Healthcare professionals or others delivering ECG assessment of QT-based cardiac risk, in settings applicable to the above population (training and workflow)[b]	Any UK population[b]	People starting or maintained on antipsychotic medications that are associated with QT prolongation, in whom an ECG assessment of QT-based cardiac risk is indicated
Setting:	Any setting				
Interventions (index test):	KardiaMobile 6L				Any ECG device
Comparators:	None	12-lead ECG or no ECG	12-lead ECG or no comparator		Any other ECG device or no

					ECG
Reference standard:	12-lead ECG	Not applicable			
Outcomes:	Diagnostic accuracy (the numbers of true positive, false negative, false positive and true negative test results), where the target condition is QT prolongation, determined by 12-lead ECG Secondary outcomes[c]: concordance (of QT interval determined by KardiaMobile 6L with that determined by 12-lead ECG), test failure rates and reasons for failure	Cardiac outcomes (arrhythmias, sudden cardiac death), psychiatric outcomes (to be confirmed at final scope), hospitalisations (cardiac of psychiatric), referrals to mental health crisis teams, other adverse effects of antipsychotic medication, HRQoL Secondary outcomes[c]: change to treatment decision, time from decision to prescribe to treatment	Secondary outcomes[c]: measures of service user preference (e.g., rates of refusal or missed appointments), number of 12-lead ECGs required, number of cardiology referrals/requests for cardiology interpretation, appointment length (including time to take ECG and time for general care of the service user), ease of use (for service users and healthcare professionals), including training requirements, cleaning of the device between uses and time to obtain ECG	Secondary outcomes[c]: costs related to use of devices (including purchase costs, software subscriptions and consumable costs), costs related to doing the tests (including staff time for travel, and time for testing and interpretation), cost of training (including operating ECG devices and interpreting ECG outputs), cost of treatment (including treatment of any cardiac or psychiatric conditions), cost of missed appointments	Quality-Adjusted Life Years
Study design:	Diagnostic cohort studies or observational, non-inferiority/equivalence studies for concordance	RCTs, CCTs or observational before and after (implementation) studies	RCTs, CCTs and comparative or non-comparative observational studies		Studies reporting a full economic analysis

[a]The assessment will include a pragmatic review of costs studies, with studies being included based on a judgement of likely relevance to the UK setting; a full systematic review of costs studies will not be undertaken

[b]Evidence from other populations, outside the scope for this assessment, will be considered and the relevance/applicability of any such evidence to the scope will be discussed

[c]Outcomes which are not sufficient to inform decision making about routine use in UK NHS clinical practice, in the absence of higher-level outcomes data (evidence about the

clinical efficacy and safety of the device), but which may inform consideration of the potential benefits of the intervention and future research decisions

3.2 Search strategy

Search strategies will be undertaken to identify studies evaluating KardiaMobile 6L (as described in Table 1), as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[18] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[20]

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase EMTREE), and existing reviews identified during the initial scoping searches. Strategy development will involve an iterative approach, testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords and thesaurus terms will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations (Ovid)
- MEDLINE Daily Update (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (Internet) (https://www.crd.york.ac.uk/CRDWeb/)
- Health Technology Assessment Database (HTA) (Internet) (https://www.crd.york.ac.uk/CRDWeb/
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO)
- PsycINFO (OvidSP)
- KSR Evidence (KSR Ltd)
- Epistemonikos (Internet) (https://www.epistemonikos.org/)
- International HTA database (INAHTA) Publication (Internet) (https://www.inahta.org/hta-database/)
- NIHR Health Technology Assessment Programme (Internet) (https://www.nihr.ac.uk/)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) (http://www.crd.york.ac.uk/prospero/)
- International Platform of Registered Systematic Review and Meta-analysis Protocols (Internet) (Home - INPLASY)
- Latin American and Caribbean Health Sciences Literature (LILACS) (Internet) (http://regional.bvsalud.org/php/index.php?lang=en)

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov/)
- EU Clinical Trials Register (Internet) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet) (http://www.who.int/ictrp/en/)
- ScanMedicine (Internet) (https://scanmedicine.com/)

To identify conference proceedings, searches in Embase will not be restricted to exclude conference abstracts. In addition, a search will be undertaken of the following conference proceedings resource:

- Northern Light Life Sciences Conference Abstracts (Ovid)

Key conference proceedings, not indexed in either Embase or Northern Light and identified in consultation with clinical experts may also be screened for the last five years.

An additional search of the medRxiv PrePrint server will be undertaken. All results retrieved from this resource will be treated with due caution as these are preliminary reports of work that have not been certified by peer review.

- MedRxiv (Internet) (https://www.medrxiv.org)

No restrictions on language, publication status or date will be applied. Searches will include generic and other product names for the intervention.

The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist based on the CADTH Peer Review checklist.[21]

References in retrieved articles will be checked for additional studies to identify any additional relevant papers not retrieved by the searches and clinical experts will be consulted to identify ongoing or un-published studies.

Additional literature searches will be performed with the aim of identifying any published economic evaluations of ECG assessment of QT-interval-based cardiac risk in service users prior to the initiation of antipsychotic medications or for monitoring QT-interval-based cardiac risk once medication has been established. This review will not be restricted by ECG device, since model structures used to evaluate the cost effectiveness of 12-lead ECG are likely to be relevant to future evaluations of KardiaMobile 6L or other mobile devices. A methodological study design filter to identify cost and economic studies in databases that are not health economic specific will be included in the search strategy for economic evaluations. The following databases and resources will be searched to identify economic evaluations:

- MEDLINE (Ovid)

- MEDLINE In-Process Citations (Ovid)
- MEDLINE Daily Update (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- CEA Registry (Internet) (http://www.cearegistry.org)
- Research Papers in Economics (RePEc) (Internet) (http://repec.org/)

The results of these additional searches will also be screened for relevant costs studies.

Example search strategies are presented in Appendix 1. These may be adapted following consultation with clinical experts.

3.3 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participant characteristics (e.g. demographic characteristics, presenting symptoms/diagnosis, other cardiac risk factors, antipsychotic medication being initiated or which is the indication for monitoring, etc.), details of the implementation of KardiaMobile 6L (protocol for use, definition of abnormal QTc used, method of reporting output, experience and training of healthcare professionals administering the ECG and of those interpreting the output, etc.), application (baseline screening or monitoring), details of reference standard (12-lead ECG) including where and by whom this was performed and interpreted, measures of test accuracy (e.g. sensitivity and specificity) and test technical performance outcome measures (e.g. failure rate and reasons for test failure, concordance), cardiac outcomes (arrhythmias, sudden cardiac death), psychiatric outcomes, hospitalisations (cardiac or psychiatric), other adverse effects of antipsychotic medication, HRQoL, changes to treatment decision, number of 12-lead ECGs required, time from decision to prescribe to treatment, measures of service user preference (e.g. rates of refusal or missed appointments), and workflow and training outcomes (e.g. number of cardiology referrals/requests for cardiology interpretation, appointment length, training requirements). Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

The assessment will include a pragmatic review of costs studies, with studies being included based on a judgement of likely relevance to the UK setting; a full systematic review of costs studies will not be undertaken. A list will be provided of any relevant cost effectiveness

studies (see Table 1) identified; no data extraction or quality assessment of these studies will be undertaken.

3.4 Quality assessment strategy

The methodological quality of any included RCTs will be assessed using the Cochrane Risk of Bias Tool.[22] Diagnostic accuracy studies will be assessed using QUADAS-2.[23] The methodological quality of other study designs will be assessed using topic-specific criteria or published tools, as appropriate. The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

3.5 Methods of synthesis/analysis

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed, by study population/patient group (e.g. presenting symptoms/diagnosis and type of antipsychotic medication, type and experience of healthcare professional), and outcome type (primary or secondary) and specific outcome reported. For studies conducted in other populations, outside the scope for this assessment, a discussion of the relevance/applicability of study results to the research questions defined in the scope will be provided. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results.

If sufficient data are available, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of KardiaMobile 6L, for the detection of QT prolongation, in each specified patient group will be calculated. The bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model will be used to generate summary estimates and an SROC curve.[24-26] If more than one comparative clinical trial, of similar study design, evaluates the same clinical outcome in the same patient group, assessed using a similar KardiaMobile 6L protocol and comparator (12 lead ECG or no ECG), then data will be pooled on treatment effect (e.g. hazard ratio, odds ratio, relative risk, weighted mean difference). The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs.

Where there is insufficient evidence to assess the clinical efficacy and safety of implementing the KardiaMobile 6L, the available evidence on the potential benefits of

implementing the KardiaMobile 6L device (as specified in the scope) will be summarised, to inform decisions about whether further research to establish clinical efficacy and safety is warranted. A detailed description of evidence gaps will be provided, in the context of the requirements for a full diagnostic assessment (including cost effectiveness modelling). Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

4 Methods for identifying and reviewing published cost-effectiveness studies

Additional literature searches will be performed with the aim of identifying any published economic evaluations of ECG assessment of QT-interval-based cardiac risk in service users prior to the initiation of antipsychotic medications or for monitoring QT-interval-based cardiac risk once medication has been established. This review will not be restricted by ECG device, since model structures used to evaluate the cost effectiveness of 12-lead ECG are likely to be relevant to future evaluations of KardiaMobile 6L or other mobile devices. A methodological study design filter to identify cost and economic studies in databases that are not health economic specific will be included in the search strategy for economic evaluations. The following databases and resources will be searched to identify economic evaluations:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations (Ovid)
- MEDLINE Daily Update (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- CEA Registry (Internet) (http://www.cearegistry.org)
- Research Papers in Economics (RePEc) (Internet) (http://repec.org/)

An example search strategy is provided in Appendix 1.

5 Handling of information from the companies

All data submitted by the manufacturers, sponsors or other stakeholders will be considered if received by the EAG no later than 15/07/2022. Data arriving after this date will be considered if practicable and at the discretion of the EAG. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in 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.

6 Competing interests of authors

None

7 Timetable/milestones

Milestones	Completion data
Draft protocol	08/02/2022
Final protocol	29/03/2022
Progress report	06/06/2022
Draft assessment report	16/06/2022
Final assessment report	27/06/2022

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Appendix 1

Clinical Effectiveness: example search strategy

Embase (Ovid): 1974-2022/03/15
Searched 16.3.22

6L ECGs or named KardiaMobile (NoA)

1 (portable or hand?held or 6?lead$ or lead?6 or leads?6 or six?lead or six?channel$ or 6?channel$ or 6l or 6?l).ti,ab,ot,hw. (59225)
2 exp Electrocardiogram/ or exp electrocardiography/ or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (398727)
3 1 and 2 (1860)
4 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (2369)
5 or/3-4 (4149)
6 animal/ (1560913)
7 animal experiment/ (2787118)
8 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (7199547)
9 or/6-8 (7199547)
10 exp human/ (23383637)
11 human experiment/ (569249)
12 or/10-11 (23385655)
13 9 not (9 and 12) (5456659)
14 5 not 13 (3995)
15 (letter or editorial or note).pt. (2822181)
16 14 not 15 (3794)

Cost effectiveness: example strategy

Embase (Ovid): 1974 to 2022/03/14
Searched 15.3.22

Antipsychotics + ECGs + Costs (No A)

1 exp neuroleptic agent/ or exp atypical antipsychotic agent/ or (antipsycho$ or anti-psycho$ or neuroleptic$).ti,ab,ot. (287399)
2 ((major or butyrophenone) adj3 (tranquiliz$ or tranquilis$)).ti,ab,ot. (268)
3 (pimozide or antalon or r 6238 or opiran or orap or pimocide or pimoride or pimozide or pizide or "2062−78−4").ti,ab,ot,hw,rn. (8382)
4 (Amisulpride or aktiprol or amilia or aminosultopride or amiprid or amisan or amissulprida or amisulgen or amisulid or amisulpiride or amisulpisan or amisulprid or amisulprida or amisulpridlich or amisulpridum or amitrex or amsulgen or apd 421 or apd421 or aposuprid or aracalm or barhemsys or dan 2163 or dan2163 or deniban or isofredil or nodasic or pridosil or sertol or socian or solian or sulamid or sulpitac or "71675−85−9" or "81342−13−4").ti,ab,ot,hw,tn. (6263)
5 (Chlorpromazine or 2601 a or 4560 r p or aminasin or aminasine or aminazin or aminazine or ampliactil or amplictil or ancholactil or aspersinal or bellacina or cepezet or chlomazine or chlorpromazine or chlor pz or chloractil or chlorbromasin or chlordelazine or chlorderazin or

chlormazine or chloropromazine or chlorpromanyl or chlorpromazine or chlorpromed or clonazine or clordelazin or clorpromaz or chlorpromazine or clozine or contomin or Duncan or elmarin or esmino or fenactil or hibanil or hibernal or hibernol or hl 3746 or hl 5746 or klorproman or klorpromazin or klorpromex or laractyl or largactil or largactyl or matcine or megaphen or megatil or ml 5746 or neomazine or neurazine or novomazina or phenethyl or plegomazin or plegomazine or proma or promacid or promactil or promapar or promazil or promexin or propaphen or propaphenin or prozil or prozin or psychozine or psynor or rp 4560 or sanopron or skf 2601 a or solidon or sonazine or taroctil or taroctyl or thor prom or thorazene or thorazine or torazina or vegetamin a or vegetamin b or winsumin or wintamine or wintermin or zuledin or "50−53−3" or "69−09−0").ti,ab,ot,hw,tn. (51345)

6 (Haloperidol or alased or aloperidin or aloperidine or "apo−haloperidol" or avant or benison or brotopon or celenase or cereen or cerenace or cizoren or depidol or dores or dozic or duraperidol or einalon s or fortunan or govotil or haldol or halidol or "halo−p" or halojust or halomed or haloneural or haloper or haloperil or haloperin or haloperitol or halopidol or halopol or halosten or haricon or "haridol−d" or keselan or linton or "lodomer−2" or mcn jr 1625 or mcn jr1625 or mixidol or novoperidol or nsc 170973 or nsc170973 or peluces or perida or peridol or peridor or r 1625 or r1625 or selezyme or seranace or serenace or serenase or serenelfi or siegoperidol or sigaperidol or "trancodol−10" or "trancodol−5" or "1511−16−6" or "52−86−8").ti,ab,ot,hw,tn. (66521)

7 (levomepromazine or "apo−methoprazine" or bayer 1213 or cl 36467 or cl 39743 or cl36467 or cl39743 or hirnamin or l mepromazine or levium or levo mepromazine or levo promazine or levomeprazine or levopromazin or levopromazine or levoprome or levozin or mepromazine or methotrimeprazine or methotrimeprazine or methozane or milezin or minozinan or neozine or neuractil or neurocil or nirvan or nozinan or rp 7044 or rp7044 or sinogan or skf 5116 or skf5116 or tiscerin or tisercin or veractil or "1236−99−3" or "60−99−1" or "7104−38−3").ti,ab,ot,hw,tn. (5665)

8 (quetiapine or alcreno or alzen or atrolak or biquelle or desiquet or ici 204636 or ici 204646 or ici204636 or ici204646 or ketileppt or ketilept or ketipinor or kvelux or kventiax or psicotric or quetex or quetiapine or quetiapine or seresano or seroquel or setinin or socalm or tienapine or tomel or xeroquel or "111974−72−2").ti,ab,ot,hw,tn. (26399)

9 (aripiprazole or abilify or abilitat or opc 14597 or opc 31 or opc14597 or opc31 or "129722−12−9").ti,ab,ot,hw,tn. (17885)

10 (Asenapine or org 5222 or org5222 or saphris or secuado or sycrest or "65576−45−6" or "85650−56−2").ti,ab,ot,hw,tn. (1791)

11 (clozapine or alemoxan or azaleptin or clopine or clopsine or clozapine or clozaril or denzapine or dorval or dozapine or elcrit or fazaclo or hf 1854 or hf1854 or lapenax or leponex or lozapin or lozapine or sizopin or versacloz or zapen or zaponex or "5786−21−0").ti,ab,ot,hw,tn. (36363)

12 (Flupentixol or flupenthixol or flupenthixole or emergil or fluanxol or flurentixol or fluxanxol or lc 44 or lc44 or n 7009 or n7009 or siplaril or siplarol or "2413−38−9" or "2709−56−0").ti,ab,ot,hw,tn. (5875)

13 (Loxapine or adasuve or "alxz 004" or alxz004 or "az 004" or az004 or cl 62,362 or cl 62362 or cl62,362 or cl62362 or cloxazepin or cloxazepine or "int 0036" or int0036 or loxapane or loxapin or loxitane or oxilapine or sum 3170 or sum3170 or "1977−10−2" or "54810−23−0").ti,ab,ot,hw,tn. (2825)

14 (Prochlorperazine or 6140 rp or antinaus or bayer a 173 or bayer a173 or capazine or chlormeprazine or chlorpeazine or chlorperazine or compro or dicopal or emelent or klometil or kronocin or meterazine or metherazine or nautisol or nipodal or normalmin or pasotomin or prochlor or prochlorpemazine or prochlorperacine or prochlorperzine or prochlorpromazine or proclorperazine or rp 6140 or rp6140 or skf 4657 or skf4657 or tementil or temetil or "58−38−8").ti,ab,ot,hw,tn. (6751)

15 (Olanzapine or anzatric or dopin tab or jolyon md or lanopin or lanzac or ly 170053 or ly170053 or meltolan or midax or olace or oladay or olan or olandus or olanex or olansek or olapin or olazax or

oleanz or olexar or oltal or olzap or onza or ozapin md or psychozap or relprevv or zalasta or zelta or zypadhera or zyprex or zyprexa or zyprexav or "132539−06−1").ti,ab,ot,hw,tn. (40263)
16 (Paliperidone or Invega or r 76477 or r76477 or ro 76477 or ro 92670 or ro76477 or ro92670 or trevicta or xeplion or "144598−75−4" or "199739−10−1").ti,ab,ot,hw,tn. (5420)
17 (Risperidone or belivon or consta or dlp 114 or dlp114 or doria or eperon or jnj 410397 or jnj410397 or "ly 03004" or ly03004 or neripros or noprenia or perseris or "r 064766" or r 64766 or r064766 or r64766 or rbp 7000 or rbp7000 or relday or riperidon or risolept or rispen or risperdal or risperdalconsta lp or risperdaloro or risperidone or risperisphere or rispid or rispolept or rispolet or rispolux neo or rizodal or sequinan or tv 46000 or tv46000 or val 401 or val401 or zargus or zofredal or "zx 003" or zx003 or "106266−06−2").ti,ab,ot,hw,tn. (40181)
18 (Sulpiride or abilit or aiglonyl or arminol or dobren or dogmatil or dogmatyl or dolmatil or eglonyl or equilid or fk 880 or fk880 or isnamide or levair or levobren or levopraid or levosulpiride or meresa or miradol or neogama or sulfiride or sulpivert or sulpyride or synedil or vipral or "15676−16−1").ti,ab,ot,hw,tn. (12939)
19 (brexpiprazole or opc 34712 or opc34712 or rexulti or rxulti or "913611−97−9").ti,ab,ot,hw,tn. (701)
20 (Cariprazine or mp 214 or mp214 or reagila or rgh 188 or rgh188 or vraylar or "1083076−69−0" or "839712−12−8" or "955400−75−6").ti,ab,ot,hw,tn. (817)
21 (Lurasidone or latuda or mk 3756 or mk3756 or sm 13496 or sm13496 or smp 13496 or smp13496 or "367514−87−2" or "367514−88−3").ti,ab,ot,hw,tn. (2084)
22 (Trifluoroperazine or calmazine or eskazine or eskazinyl or espazine or fluoperazine or fluperin or flurazin or "iremo−pierol" or jatroneural or leptazine or modalina or modiur or nerolet or nylipton or operzine or oxyperazine or psyrazine or skf 5019 or sporalon or stelazine or terfluzin or terfluzine or triflumed or trifluoperazide or trifluoperzine or trifluoroperazine or trifluorperacine or trifluorperazine or trifluperazine or triflurin or triftazin or triftazine or triftazinum or trinicalm or triozine or triphtazine or triphthasine or triphthazine or "117−89−5" or "440−17−5").ti,ab,ot,hw,tn. (1056)
23 (Zuclopenthixol or cis clopenthixol or cisordinol or sedanxol or z clopenthixol or "53772−83−1").ti,ab,ot,hw,tn. (2909)
24 or/1-23 (307718)
25 exp Electrocardiogram/ or exp electrocardiography/ or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (398625)
26 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (2366)
27 (CardioSecur or "Personal MedSystems GmbH").ti,ab,ot,hw. (9)
28 (D-Heart or "D Heart").ti,ab,ot,hw. (367)
29 ("RhythmPad GP" or CurAlive).ti,ab,ot,hw. (1)
30 or/25-29 (400626)
31 24 and 30 (6442)
32 health-economics/ (34104)
33 exp economic-evaluation/ (330916)
34 exp health-care-cost/ (315403)
35 exp pharmacoeconomics/ (217091)
36 or/32-35 (699911)
37 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1233575)
38 (expenditure$ not energy).ti,ab. (45662)
39 (value adj2 money).ti,ab. (2715)
40 budget$.ti,ab. (43059)
41 or/37-40 (1274210)
42 36 or 41 (1619827)

43 letter.pt. (1214750)
44 editorial.pt. (719945)
45 note.pt. (886606)
46 or/43-45 (2821301)
47 42 not 46 (1492310)
48 (metabolic adj cost).ti,ab. (1698)
49 ((energy or oxygen) adj cost).ti,ab. (4737)
50 ((energy or oxygen) adj expenditure).ti,ab. (34619)
51 or/48-50 (39892)
52 47 not 51 (1484125)
53 exp animal/ (28290870)
54 exp animal-experiment/ (2811330)
55 nonhuman/ (6828655)
56 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6104108)
57 or/53-56 (30392096)
58 exp human/ (23374806)
59 exp human-experiment/ (569308)
60 58 or 59 (23376875)
61 57 not (57 and 60) (7016295)
62 52 not 61 (1346232)
63 31 and 62 (255)