NICE National Institute for Health and Care Excellence

Diagnostics Assessment Programme

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Contents:

1. **Early Value Assessment Report** produced by Kleijnen Systematic Reviews Ltd (KSR)

2. **Cost and Resources Report** produced by King's Technology Evaluation Centre (KiTEC)

3. Overview

4. Stakeholder comments on the Early Value Assessment Report and KSR responses

5. Stakeholder comments on the Cost and Resources Report and KiTEC responses.

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

A Diagnostic Early Value Assessment Report commissioned by
the National Institute for Health Research Evidence Synthesis Programme
on behalf of the National Institute for Health and Care Excellence

Kleijnen Systematic Reviews Ltd

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Contributions of authors

Marie Westwood and Pawel Posadzki planned and performed the systematic review and interpretation of evidence. Nigel Armstrong contributed to planning and interpretation of the systematic review. Caro Noake devised and performed the literature searches and provided information support to the project. All parties were involved in drafting and/or commenting on the report.

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ABSTRACT

Background

The primary indication for this assessment is the use of the KardiaMobile 6L 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.

Objectives

To provide an Early Value Assessment (EVA) of whether KardiaMobile 6L has the potential to provide an effective and safe alternative to 12-lead electrocardiogram (ECG) for initial assessment and monitoring of QT interval-based cardiac risk in people taking antipsychotic medications.

Methods

Twenty-seven databases were searched to April/May 2022. Review methods followed published guidelines. Where appropriate, study quality was assessed using appropriate risk of bias tools. Results were primarily summarised using a narrative synthesis, structured by a research question.

Results

We did not identify any studies which provided information about the diagnostic accuracy of KardiaMobile 6L, for the detection of QTc-interval prolongation, in any population. All studies which reported information about agreement between QT interval measurements (corrected and/or uncorrected) with KardiaMobile 6L versus 12-lead ECG were conducted in non-psychiatric populations (e.g. cardiac patients, COVID-19 patients), used cardiologists to interpret all ECGs and, in some instances, also applied optimised methods of interpreting ECGs (multiple reader assessment). Where reported or calculable, the mean difference in QTc between devices (12-lead ECG versus

KardiaMobile 6L) was generally small (≤10 ms) and QTc measured using KardiaMobile 6L was consistently lower than that measured using 12-lead ECG.

All information about the use of KardiaMobile 6L, in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication was taken from retrospective surveys of staff and service users who had chosen to use KardiaMobile 6L during pilots, described in two unpublished project reports.

It is important to note that both of these project reports relate to work undertaken as part of a wider AHSN pilot, which was not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

[redacted]

Conclusions

There is insufficient evidence to support a full Diagnostic Assessment evaluating the clinical and cost effectiveness of KardiaMobile 6L, in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication. The evidence to inform the aims this EVA (i.e., to assess whether the device has the potential to be clinically and cost effective) was also limited. This report includes a comprehensive list of research recommendations, both to reduce the uncertainty around this EVA and to provide the additional data needed to inform a full Diagnostic Assessment, including cost effectiveness modelling.

TABLE OF CONTENTS

Abstract 4
Table of Contents 6
List of Tables 8
List of Figures 9
List of Abbreviations 10
Scientific Summary 12
Plain English summary 16
1. Objective 17
2. Background and definition of the decision problem(s) 19
2.1 Population 19
2.1.1 Presentations for which antipsychotic medications, associated with a risk of QT prolongation, may be prescribed 20
2.2 Intervention technology 21
2.3 Target condition 23
2.4 Care pathway 24
2.4.1 Risk assessment 24
2.4.2 Management/treatment 24
3. Systematic review methods 26
3.1 Search strategy 26
3.2 Inclusion and exclusion criteria 28
3.3 Inclusion screening and data extraction 32
3. 4 Quality assessment 32
3. 5 Methods of analysis/synthesis 33
4. Systematic review results 34
4.1 Overview of included studies 36
4.2 Study quality 45
4.3 What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)? 49
4.4 What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)? 61
4.5 What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues? 62
4.6 What are the costs, from a UK NHS and PPS 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? 67
4.7 What existing, published cost effectiveness studies are available about QT interval assessment for service users who require antipsychotic medication? 69
5. Discussion 71
5.1 Statement of principal findings 71
5.2 Strengths and limitations of assessment 73
5.3 Uncertainties 75
6. Conclusions 79

6.1 Implications for service provision 79
6.2 Suggested research priorities 79
7. References 84
Appendix 1: Literature search strategies 90
Appendix 2: QUADAS-2 assessments 108
Appendix 3: Details of excluded studies with rationale 113
Appendix 4: Potentially relevant ongoing studies 122
Appendix 5: copies of staff surveys used in the CNTW pilot study 123
Appendix 6: PRISMA check list 129

LIST OF TABLES

Table 1: Inclusion criteria 29
Table 2: Overview of included studies 38
Table 3: QUADAS-2 results for technical validation studies of KardiaMobile 6L 49
Table 4: Study details for technical validation studies and case series 51
Table 5: Summary of results from technical validation studies and case series 56
Table 6: Details of studies reporting information on service user acceptability/satisfaction and on training and workflow issues 64
Table 7: Comparison of time taken to obtain an ECG using KardiaMobile 6L and using 12-lead ECG . 66
Table 8: Comparison of annual ECG costs using KardiaMobile 6L versus 12-Lead device 70
Table 9: Studies excluded based on full text screening 118

LIST OF FIGURES

Figure 1: Flow of studies through the review process 35

LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

6L	6-lead
AHSN	Academic Health Science Network
AiC	Academic in confidence
AUC	Area under the curve
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	Controlled clinical trial
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Confidence in confidential
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNTW	Cumbria, Northumberland and Tyne and Wear
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DOAJ	Directory of Open Access Journals
DPIA	Data Protection Impact Assessment (however, only used once in Table 2)
ECG	Electrocardiogram
EED	Economic Evaluation Database
ERT	eResearch Technology
EVA	Early Value Assessment
FN	False negative
FP	False positive
GDPR	General Data Protection Regulation
GP	General Practitioner
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
ID	Identification
INAHTA	International Network of Agencies for Health Technology Assessment
KSR	Kleijnen Systematic Reviews Ltd
LILACS	Latin American and Caribbean Health Sciences Literature
max	Maximum
mins	Minutes
minimum	Minimum
mm	Millimetres
ms	Milliseconds
NA	Not applicable
NENC	North East and North Cumbria
NHMRC	National Health Medical Research Council
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NR	Not reported
PDF	Portable document format
PROSPERO	International Prospective Register of Systematic Reviews
PSS	Personal Social Services
QALY	Quality-adjusted life years
QT	QT interval
QTc	Corrected QT interval
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
s	Seconds
SCMs	Specialist Committee Members
SD	Standard deviation
SOP	Standard operating procedure
SROC	Summary receiver operating characteristic
TEWV	Tees Esk and Wear Valleys
TN	True negative
TP	True positive
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

SCIENTIFIC SUMMARY

Background

The primary indication for this assessment is the use of the KardiaMobile 6L electrocardiogram (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.

Current United Kingdom (UK) guidance recommends that a person should be offered an ECG before starting antipsychotic medication if:

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

This Early Value Assessment (EVA) considers 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, this would be the case both for both assessment prior to the initiation of antipsychotic medications and for monitoring QT interval-based cardiac risk once medication has been established. 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.

Objectives

The overall aim of this project was 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-based cardiac risk assessment for service users who require antipsychotic medication.

We 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 is the accuracy/technical performance of KardiaMobile 6L, where prolonged corrected QT interval (QTc), determined by 12-lead ECG (the reference standard method) is the target condition?
- 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 are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?
- What are the costs, from a United Kingdom (UK) National Health Service (NHS) and Personal Social Services (PSS) 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 used 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 QT interval-based cardiac risk in people taking antipsychotic medications. The available evidence has been summarised, with consideration of its relevance to the above research questions, and a detailed description of evidence gaps where further research is needed is provided. This assessment does not include cost effectiveness modelling, because the evidence currently available is not sufficient to support this.

Methods

Twenty-seven databases, including MEDLINE and Embase, research registers, conference proceedings and a pre-print resource were searched for relevant studies from inception to April/May 2022. Search results were screened for relevance independently by two reviewers. Full text inclusion assessment, data extraction, and quality assessment were conducted by one reviewer and checked by a second. The methodological quality of included technical validation studies was assessed using relevant components of QUADAS-2. No formal quality assessment was applied to the other study types (case series) included in this report. We did not consider formal assessment of methodological quality or risk of bias to be appropriate for non-research study pilot project reports,

however, our report includes a qualitative summary of the key issues, with respect to the reliability of the information provided by these reports to address the aims of this EVA. Meta-analysis was considered inappropriate, due to the small number of included studies and wide variation in study design, study populations and outcomes reported; we therefore employed a narrative synthesis. The results section of this report is structured by research question.

Results

The evidence to inform this EVA of KardiaMobile 6L, for use in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication, was extremely limited.

We did not identify any studies, which addressed any of the five research questions defined for this EVA, in the target population (service users who require antipsychotic medication).

All eight included studies were technical validation studies or case series, which reported some limited information about agreement between QT interval measurements derived from KardiaMobile 6L and 12-lead ECG. All of these studies were conducted in non-psychiatric populations (e.g. cardiac patients, COVID-19 patients), and all used cardiologists to interpret all ECGs and, in some instances, also applied optimised methods of interpreting ECGs (multiple reader assessment). Where reported or calculable, the mean difference in QTc between devices (12-lead ECG versus KardiaMobile 6L) was generally small (≤10 ms) and QTc measured using KardiaMobile 6L was consistently lower than that measured by 12-lead ECG. However, it should be noted that none of the included studies provided any information to indicate in how many (if any) patients observed differences in measured QTc would have resulted in a change of clinical category.

All of the information about the use of KardiaMobile 6L in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication, included in this EVA report, was taken from two unpublished pilot project reports.

It is important to note that both of these project reports relate to work undertaken as part of a wider AHSN pilot, which was not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

[redacted]

[redacted]

Conclusions

As anticipated during the scoping phase of this assessment and reflected in the decision to undertake an EVA, there is insufficient evidence to support a full Diagnostic Assessment evaluating the clinical and cost effectiveness of KardiaMobile 6L, in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication. The evidence to inform the aims this EVA (i.e., to assess whether the device has the potential to be clinically and cost effective) was also limited. This report includes a comprehensive list of research recommendations, both to reduce the uncertainty around this EVA and to provide the additional data needed to inform a full Diagnostic Assessment, including cost effectiveness modelling.

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 General Practitioners (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 (or 6-lead) is a portable ECG that may offer a less intrusive way to take ECG measurements. This is because less undressing is needed since the electrodes are only applied to fingers of the left and right hand and the left ankle or knee 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 considers 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 provides recommendations about the research needed, so that a decision can be made about whether it should be used in the NHS in England, after further research has been completed.

1. OBJECTIVE

The overall aim of this project was 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-based cardiac risk 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 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 is the accuracy/technical performance of KardiaMobile 6L, where prolonged corrected QT interval (QTc), determined by 12-lead ECG (the reference standard method) is the target condition?
- 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 are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?
- What are the costs, from a United Kingdom (UK) National Health Service (NHS) and Personal Social Services (PSS) 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 early value assessment (EVA) used a broader scope to consider whether the KardiaMobile 6L device triage 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 included 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 have been 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 has been summarised, with consideration of its relevance to the above research questions, and a detailed description of evidence gaps where further research is needed is provided. This assessment does not include cost effectiveness modelling, because the evidence currently available is not sufficient to support this.

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Population

The primary indication for this assessment is the use of the KardiaMobile 6L 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 QTc prolongation, and for monitoring QT interval-based cardiac risk once medication has been established. The National Institute for Health and Care Excellence (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 or
- A physical examination has identified specific cardiovascular risk or
- There is a family history of cardiovascular disease, sudden collapse, or other cardiovascular risk factors such as arrhythmia or
- 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 to 5 half-lives).[4] If the service user is taking other QTc prolonging medication, or has risk factors for QTc prolongation, then regular ECG monitoring is recommended. An ECG is also recommended after dose changes.[4] The British Heart Rhythm Society clinical practice guidelines on the management of patients developing QTc prolongation on antipsychotic medication recommend that QTc is measured using either lead II or V5.[5]

This assessment considers the potential clinical effectiveness of using KardiaMobile 6L for the 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 QTc 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 QTc prolongation, identified by KardiaMobile 6L, would be followed up using 12-lead ECG, this would be the case both for both assessment prior to the

initiation of antipsychotic medications and for monitoring QT interval-based cardiac risk once medication has been established. 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.

2.1.1 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 World Health Organization (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 (psychosis in the context of severe mood disturbance such as depression or mania). 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 there were no significant differences in the 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 one 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 seven 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 QTc.[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.

2.2 Intervention technology

People taking antipsychotic medications, which are associated with an established risk of QTc prolongation, may need to be screened for QTc prolongation before initiation of treatment and monitored for the development of QTc 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 six limb leads which view the heart in a vertical plane, and six 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 (6L) ECG device that is manufactured by AliveCor. It uses three electrodes to record a person's ECG and wirelessly transmits the data to a compatible smartphone or tablet via Bluetooth. The Kardia application allows the ECG data to be converted into a portable document format (PDF). This can then be sent via email to physicians. User data are stored on a General Data Protection Regulation (GDPR)-compliant cloud-based system hosted in Frankfurt, Germany. The device is powered by a single coin cell battery.

There are two electrodes on the top of the device for use with the left and right hands, and one 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 a 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 application, 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 6L ECGs. Currently, QTc must be calculated by the user, however the company is developing software to allow automated QTc 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 6L 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.

Pacemakers (and pacemakers that are also defibrillators) effect ECG devices in that they generate sharply abnormal cardiac electrical activity, when they are active (pacing); this results in pacemaker "spikes", which are readily recognisable by a human reader, but which may cause problems for automated interpretation. The manufacturer's instructions for use, for KardiaMobile 6L, include the statement: 'DO NOT use with a cardiac pacemaker, ICDs, or other implanted electronic devices.'

2.3 Target condition

Some antipsychotic medications are associated with prolonged ventricular repolarisation, potentially giving rise to QT prolongation. In rare cases, this can lead to arrhythmias such as polymorphic ventricular tachycardia (including torsades de pointes), which can cause hypotension, with dizziness, fainting, and convulsions, and can progress to ventricular fibrillation and sudden cardiac death.[15]

The target condition, with respect to assessing the accuracy of KardiaMobile 6L, is QTc prolongation. It is important to note that the term QTc, which means corrected QT interval, is often used for QT interval, given that the QT interval needs to be corrected for heart rate. Definitions of abnormal QTc vary. According to British Heart Rhythm Society clinical practice guidelines[5] a QTc is considered normal if below 440 milliseconds (ms) for men, or below 470 ms for women. The 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. The Maudsley Prescribing Guidelines advise not to use QTc-prolonging drugs if QTc is more than 460 ms and the patient has had an unexplained syncopal episode.[16] If the QTc is between 480 ms and 499 ms, it is advised to consider alternative therapy or monitor QTc 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] recommends 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.

2.4 Care pathway

2.4.1 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 focused on the use of ECG to assess QT interval-based cardiac risk.

2.4.2 Management/treatment

During scoping discussions, clinical experts advised that changes to antipsychotic medication following detection of prolonged QTc are made following an assessment of the relative risk and benefit of treating the psychiatric condition versus cardiac side effects. 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 provides a systematic review of the evidence about the accuracy of KardiaMobile 6L, as an initial testing (triage) method for the detection of QTc 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, therefore, also considered evidence about effects of implementing KardiaMobile 6L on the rates of adverse clinical outcomes, both cardiac and psychiatric.

This assessment also considered any reported information on testing uptake 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 aimed 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-based cardiac risk assessment for service users who require antipsychotic medication. It was anticipated that currently available evidence would 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, therefore, focused 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 QT interval-based cardiac risk in people taking antipsychotic medications, such that further research to establish clinical efficacy and safety is warranted. To this end, the assessment used a broad scope and include 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 were 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. This assessment does not include cost effectiveness modelling, because the evidence currently available is not sufficient to support this.

3. SYSTEMATIC REVIEW METHODS

Systematic review methods followed 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 Search strategy

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

Candidate search terms were 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 involved 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 were developed specifically for each database and the keywords and thesaurus terms were adapted according to the configuration of each database.

The following databases were searched for relevant studies from inception to April/May 2022:

- MEDLINE (Ovid): 1946-2022/04/25
- MEDLINE In-Process Citations (Ovid): 1946-2022/04/25
- MEDLINE Daily Update (Ovid): 1946-2022/04/25
- MEDLINE Epub Ahead of Print (Ovid): 1946-2022/04/25
- EMBASE (Ovid): 1974-2022/04/25
- PubMed-not-MEDLINE (Ovid):1946-2022/05/17
- PubMed (NLM) (Internet): up to 2022/05/18
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2022/04/Iss 4
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2022/03/Iss 3
- Database of Abstracts of Reviews of Effects (DARE) (Internet)(https://www.crd.york.ac.uk/CRDWeb/): up to March 2015
- Health Technology Assessment Database (HTA) (Internet) (https://www.crd.york.ac.uk/CRDWeb/: up to March 2018
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1881-2022/04/27
- PsycINFO (Ovid): 1806-2022/04/Wk 3
- KSR Evidence (KSR Ltd)(https://ksrevidence.com/): up to 2022/04/26
- Epistemonikos (Internet) (https://www.epistemonikos.org/): up to 2022/04/27
- International HTA database (INAHTA) Publication (Internet) (https://www.inahta.org/hta-database/): up to 2022/04/27
- NIHR Health Technology Assessment Programme (Internet) (https://www.nihr.ac.uk/): up to 2022/04/27
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) (http://www.crd.york.ac.uk/prospero/): up to 2022/04/26

- International Platform of Registered Systematic Review and Meta-analysis Protocols (Internet) (https://inplasy.com/): up to 2022/04/27
- Latin American and Caribbean Health Sciences Literature (LILACS) (Internet) (http://regional.bvsalud.org/php/index.php?lang=en): up to 2022/04/28
- Directory of Open Access Journals (DOAJ) (https://doaj.org/): up to 2022/05/25
- European Heart Journal – Digital health (https://academic.oup.com/ehjdh/): up to 2022/05/19

Completed and ongoing trials were identified by searching the following resources:

- National Institutes of Health (NIH) ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov/): up to 2022/04/27
- EU Clinical Trials Register (Internet) (https://www.clinicaltrialsregister.eu/ctr-search/search): up to 2022/04/27
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Internet) (http://www.who.int/ictrp/en/): up to 2022/04/28
- ScanMedicine (Internet) (https://scanmedicine.com/): up to 2022/04/27

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

- Northern Light Life Sciences Conference Abstracts (Ovid): 2010 -2022/Week 16.

An additional search of the medRxiv PrePrint server was undertaken. All results retrieved from this resource were treated with due caution as these are preliminary reports of work that have not undergone peer review.

- medRxiv (Internet) (https://www.medrxiv.org): up to 2022/04/27.

No restrictions on language, publication status or date were applied. Searches included generic and other product names for the device where appropriate.

All search strategies are presented in Appendix 1.

The main Embase strategy for each search was independently peer reviewed by a second Information Specialist based on the Canadian Agency for Drugs and Technologies in Health (CADTH) Peer Review checklist.[21] References in retrieved articles were checked for additional studies to identify any additional relevant papers not retrieved by the searches and clinical experts were consulted to identify ongoing or unpublished studies.

Further additional literature searches were 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 was not 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 was included in those in databases that are not health economic specific. The following databases and resources were searched to identify economic evaluations:

- MEDLINE (Ovid): 1946-2022/04/26
- MEDLINE In-Process Citations (Ovid): 1946-2022/04/26
- MEDLINE Daily Update (Ovid): 1946-2022/04/26
- MEDLINE Epub Ahead of Print (Ovid): 1946-2022/04/26
- EMBASE (Ovid): 1974-2022/04/26
- NHS Economic Evaluation Database (NHS EED) (CRD): up to March 2015
- CEA Registry (Internet) (http://www.cearegistry.org): up to 2022/04/28
- Research Papers in Economics (RePEc) (Internet) (http://repec.org/): up to 2022/04/28

All search strategies are presented in Appendix 1.

3.2 Inclusion and exclusion criteria

Separate inclusion criteria were developed for each research question. These are summarised in Table 1.

Table 1: Inclusion criteria

Question	**1) What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?**	**2) What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?**	**3) What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?**	**4) 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]**	**5) 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

Question	**1) What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?**	**2) What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?**	**3) What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?**	**4) 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]**	**5) What existing, published cost effectiveness studies are available about QT interval assessment for service users who require antipsychotic medication?**
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	NA			
Outcomes:	Diagnostic accuracy (the numbers of TP, FN, FP and TN test results), where the target condition is QTc prolongation, determined by 12-lead ECG. Secondary outcomes[c]: concordance (of QTc or QT 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, hospitalisations (cardiac or 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,	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	QALYs

Question	**1) What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?**	**2) What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?**	**3) What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?**	**4) 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]**	**5) What existing, published cost effectiveness studies are available about QT interval assessment for service users who require antipsychotic medication?**
			cleaning of the device between uses and time to obtain ECG.	or psychiatric conditions), cost of missed appointments.	
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.

CCTs = controlled clinical trials; ECG = electrocardiogram; FN = false negative; FP = false positive; HRQoL = health-related quality of life; NA = not applicable; NHS = National Health Service; QALY = quality-adjusted life year; RCT = randomised controlled trial; TN = true negative; TP = true positive; UK: United Kingdom

3.3 Inclusion screening and data extraction

Two reviewers (Marie Westwood [MW] and Pawel Posadzki [PP]) independently screened the titles and abstracts of all reports identified by the searches and any discrepancies were resolved by discussion. Full copies of all studies deemed potentially relevant, after discussion, were obtained and two reviewers (MW and PP) independently assessed these for inclusion; any disagreements were resolved by discussion.

Where available, data were 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, health related quality of life (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 was extracted by one reviewer (MW) and checked by a second reviewer (PP); any disagreements were resolved by discussion.

The assessment also included scoping searches to identify costs studies KardiaMobile 6L likely to be of relevance to the UK setting (research question 4) and cost effectiveness studies about ECG QT interval assessment for service users who require antipsychotic medication; a full systematic review of costs studies and cost effectiveness studies was outside the scope of this assessment.

3. 4 Quality assessment

There is no published, validated tool for the assessment of the methodological quality of technical validation studies of diagnostic technologies; the methodological quality of these studies, therefore, assessed using the relevant components of QUADAS-2.[22] No formal quality assessment was applied to the other study types (case series) included in this report, because the size and design of these studies renders formal quality assessment inappropriate and because they have not substantially

informed the aims of this EVA. We did not consider formal assessment of methodological quality or risk of bias to be appropriate for non-research study pilot project reports, however, our report includes a qualitative summary of the key issues, with respect to the reliability of the information provided by these reports to address the aims of this EVA (Section 4.2). The results of all quality assessment processes have been 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 was undertaken by one reviewer (MW) and checked by a second reviewer (PP); any disagreements were resolved by discussion.

The results of the quality assessments are summarised and presented in tables (Section 4.2) and, for QUADAS-2 assessments, are presented in full, in Appendix 2.

3. 5 Methods of analysis/synthesis

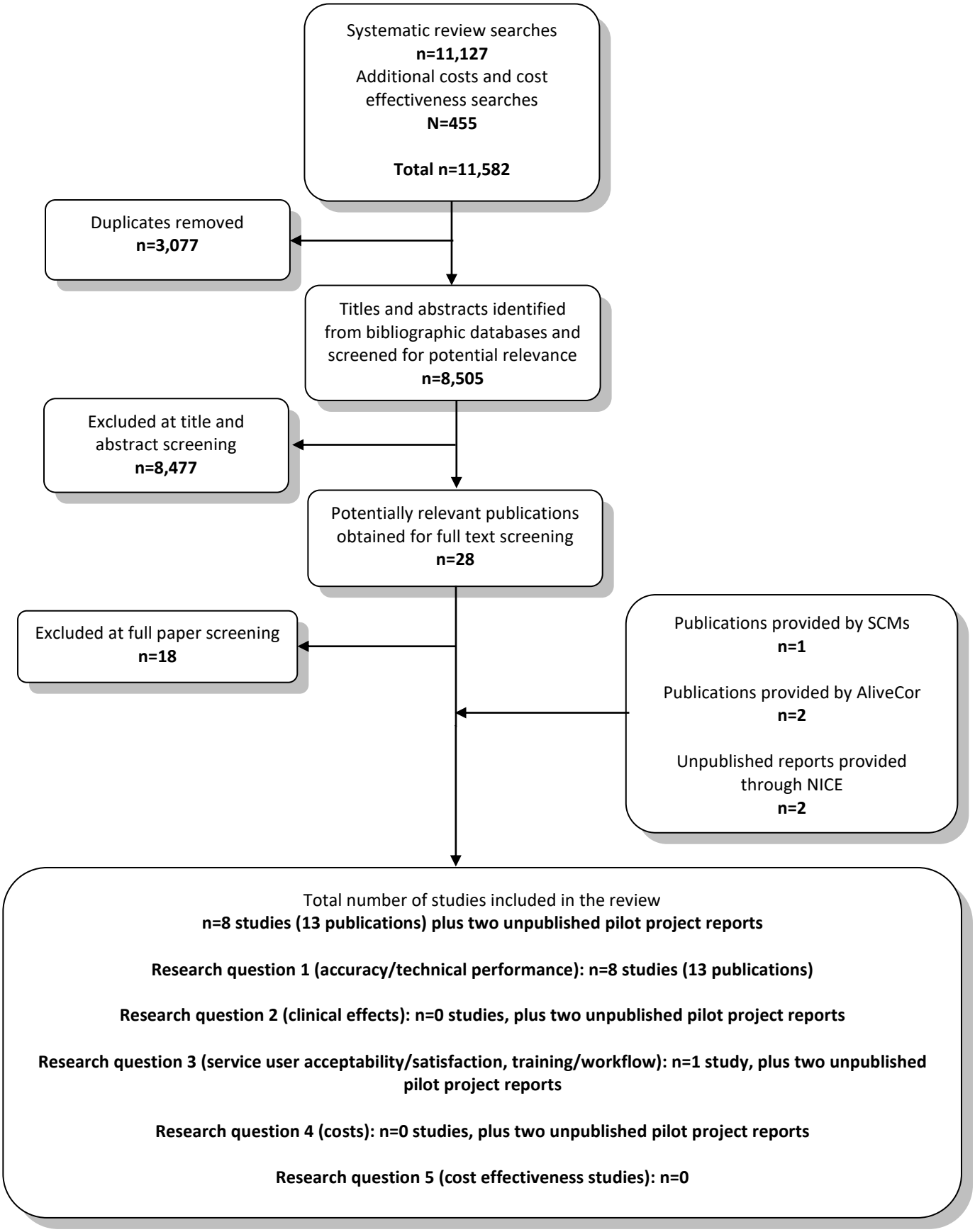
Meta-analysis was considered inappropriate, due to the small number of included studies and wide variation in study design, study populations and outcomes reported; we therefore employed a narrative synthesis. The results section of this report is structured by research question. A detailed commentary on the major methodological problems or biases that affected the studies is also provided, together with a description of how this may have affected the individual study results and the relevance or otherwise of these studies to the decision problem specified. The evidence gaps identified have been used to inform recommendations for future research.

4. SYSTEMATIC REVIEW RESULTS

The literature searches of bibliographic databases conducted for this EVA systematic review, including additional scoping searches conducted to identify costs and cost effectiveness studies, identified 8,505 unique references. After initial screening of titles and abstracts, 28 references[23-50] were considered to be potentially relevant and ordered for full paper screening; of these 10 publications,[25, 30, 33, 36, 38-43] relating to six studies, were included in the review. A further three publications, one provided by NICE/Specialist Committee Members (SCMs)[14] and two provided by the manufacturer of KardiaMobile 6L, AliveCor,[51, 52] were assessed and included in the review. These publications related to two additional studies and were all published in a journal, *European Heart Journal - Digital Health*, which is not yet indexed in the bibliographic databases searched. All other potentially relevant studies cited in documents supplied by the test manufacturer, AliveCor, had already been identified by bibliographic database searches. Finally, two unpublished project reports of pilots of KardiaMobile 6L, conducted at Tees Esk and Wear Valleys (TEWV) NHS Foundation Trust[53] and Cumbria, Northumberland and Tyne and Wear (CNTW) NHS Foundation Trust,[54] and provided through NICE, were included in the review. Figure 1 shows the flow of studies through the review process. Appendix 3 provides details, with reasons for exclusion, of all publications excluded at the full paper screening stage.

In addition to the studies included in this report, our searches of trial registries identified five potentially relevant ongoing studies; details of these studies and their current status are provided in Appendix 4.

Figure 1: Flow of studies through the review process



4.1 Overview of included studies

Based on the searches and inclusion screening described above, 13 publications,[14, 25, 30, 33, 36, 38-43,51, 52] relating to eight studies, and two additional unpublished reports,[53, 54] were included in this review; the results section of this report cites studies using the primary publication only.

All eight[14, 25, 30, 36, 40, 41,51, 52] of the included studies were published, in full, in peer-reviewed journals.

All eight of the included published studies were technical validation studies[14, 30, 36, 40, 51] or case series,[25, 41, 52] reporting some, very limited information relevant to research question 1, *'What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?'* One study[36] reported data (time to register an ECG) relevant to research question 3 *'What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?'* Although it did not meet the inclusion criteria for this question, because it was not conducted in service users requiring antipsychotic medication, data from this study have been included the results for research question 3, for completeness.[36]

The two unpublished pilot project reports provided some information relevant to research question 3, as well as some information on UK-relevant costs.[53, 54]

We did not identify any studies which specifically addressed research question 2, *'What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?'* Both the unpublished pilot project reports provided small amounts of information for the survey question, to healthcare professionals, *'Did the use of the AliveCor KardiaMobile 6L device change the clinical outcome for your patient?'*[53, 54] Finally, we did not identify any cost effectiveness studies about ECG QT interval assessment for service users who require antipsychotic medication (research question 5).

Four of the eight published studies included in this report were conducted in Europe; two were conducted in the UK,[14, 41] one in Poland[51] and one in Spain.[36] The remaining four studies were conducted in the United States of America (USA)[25, 30, 52] and in Australia.[40]

Only four[14, 25, 30, 40] of the included published studies provided any information about funding and, of these, two indicated support from AliveCor;[25, 30] details of all reported funding sources are provided in Table 2.

Both of the two unpublished project reports related to an initial pilot[53] and subsequent extended pilot project[54] conducted in the UK NHS and funded by NHSX, via the Academic Health Science Network North East and North Cumbria (AHSN NENC).

It is important to note that both of these project reports relate to work undertaken as part of a wider AHSN pilot, they were not formal research projects and were not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

Further details of the characteristics of study participants and details of the conduct of the index test (KardiaMobile 6L) and reference standard/comparator (12-lead ECG) are provided in Tables 4 and 6.

Table 2: Overview of included studies

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
Azram 2021 (EVALECG Cardio)[14]	Prospective study of 1,015 cardiology inpatients and outpatients Full paper Single centre, tertiary care cardiology Country: UK Funded by: NR; two authors received funding from Biosense Webster	To compare the diagnostic ability of the KardiaMobile 6L against the 12-lead ECG.	No	Observational technical validation study. Mean difference for QT and QTc measurements between KardiaMobile 6L ECG and 12-lead ECG, proportion of leads in which QT/QTc measurements could be performed, AUC for detection of abnormal QT interval.
Frisch 2021[25]	Prospective study of four COVID-19–positive inpatients, requiring ECG monitoring Full paper Single centre, university hospital Country: USA	To assess the feasibility of recording using, KardiaMobile 6L, along with a tablet application (KardiaStation; AliveCor) in inpatients needing intermittent ECG monitoring, and to document the ease of use of con-tactless ECG recordings and to compare contactless ECG recordings from the KardiaMobile 6L with	No	Case series QT and QTc intervals, per patient and per device.

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
	Funded by: Editing, manuscript review, formatting, reference checks, and submission preparation were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by AliveCor. Demonstration devices for this project were provided by AliveCor.	standard ECG recordings.		
Kleiman 2021[30]	Prospective study of 705 patients referred to a genetic heart rhythm clinic Full paper Single centre, tertiary care cardiology Country: USA Funded by: The research did not receive any specific grant from funding agencies in the public,	To compare recordings from the KardiaMobile 6L device to ECGs collected with standard 12-lead ECG devices.	No	Observational technical validation study. Absolute values and mean and median difference for QT and QTcF[a] measurements between KardiaMobile 6L ECG and 12-lead ECG, and categorical difference data.

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
	commercial, or not-for-profit sectors, however, one of the authors was an employee of AliveCor.			
Krzowski 2021[51]	Prospective study of 98 cardiology patients Full paper Single centre, university hospital Country: Poland Funded by: NR	To evaluate the usability of portable ECG recorders (KardiaMobile 6L (KM) and Istel (IS) HR-2000) by comparing rhythm and basic ECG parameters (PQ, RR and QT intervals, duration of QRS complexes, etc.) obtained with KM/IS to standard 12-lead ECG tracings.	No	Observational technical validation study. Mean QT measurements for KardiaMobile 6L ECG and 12-lead ECG.
Minguito-Carazo 2021[36]	Prospective study of 182 patients hospitalised with COVID-19 (within patient comparison of KardiaMobile 6L and 12-lead ECG was only undertaken for a consecutive cohort of 45 healthy patients) Full paper	To evaluate the feasibility of QTc monitoring with KardiaMobile 6L in COVID-19 patients receiving QTc-interfering therapies.	No	Observational technical validation study. Absolute values and mean difference for QTc measurements between KardiaMobile 6L ECG and 12-lead ECG, number of unreadable ECGs, and mean time

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
	Single centre, university hospital cardiology department Country: Spain Funded by: NR			taken to register ECG.
Orchard 2021[40]	Prospective study of 30 healthy athletes Full paper Single centre, university hospital Country: Australia Funded by: Authors were supported by an Australian Government Research Training Program scholarship and a NHMRC Practitioner Fellowship	To examine and compare the level of similarity between resting 6L and 12-lead readings in athletes with a view to building evidence for the utility of the 6L-ECG as a practical and accurate clinical tool in athletic populations.	No	Observational technical validation study. Absolute values and mean difference for QT and QTc measurements between KardiaMobile 6L ECG and 12-lead ECG.
Puranik 2022[41]	Prospective study of 13 patients with multi-drug resistant tuberculosis and non-tuberculous mycobacterium infections	Not stated	No	Pilot study. Mean percentage difference and

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
	Full paper Single centre, university hospital Country: UK Funded by: NR			correlation coefficient between automated 12-lead readings and manually calculated KardiaMobile readings, for QTc (concordance).
Shah 2021[52]	Prospective study of three patients undergoing antiarrhythmic drug loading at home, during COVID-19 social distancing Full paper Single centre, university hospital Country: USA Funded by: NR	To test the hypothesis that existing digital health technologies and virtual communication platforms could provide EM and support medically guided AAD loading for patients with symptomatic tachyarrhythmia in the ambulatory setting, while reducing physical contact between patient and healthcare system.	No	Pilot study. Absolute values and difference in QTc, per patient, pre- and post-loading, using KardiaMobile 6L and 12-lead ECG (concordance).
Tees and Esk and Wear Valleys NHS Foundation Trust 2021[53]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
	[redacted]			[redacted]
Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust 2021[54]	Roll out project, during which 51 ECGs were completed using KardiaMobile 6L (06/04/2021 to 31/08/2021), by an unclear number of healthcare professionals Unpublished pilot project report	Not a research study Initially, the project was to: • Set up and configure the AliveCor KardiaMobile devices and develop a DPIA to ensure the AliveCor KardiaMobile device was set up, following the Trust protocol and policies	Yes	Retrospective survey of healthcare professionals and service users. Numbers of cardiology referrals/12-lead ECGs required, comparison of time estimated mean time taken per ECG with

Study ID	Study details	Objective	Does the study include 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?	Study design and outcome(s) extracted
	Country: UK Funded by: NHSX, AHSN NENC	• Use TEWV's training materials and SOP • Complete the KardiaMobile ECG usage and submit to AHSN on a monthly basis • Liaise with the medical device team to ensure the AliveCor KardiaMobile devices were appropriately recorded and asset ID • Support pilot teams		KardiaMobile 6L compared to 12-lead ECG (staff estimates), comparison of estimated costs, qualitative data on service user and healthcare professional preferences, and changes to service user care.

[a]The correction method used (Fridericia or Framingham) was not reported in the paper

6L – 6-lead; AAD = antiarrhythmic drug loading; AHSN = Academic Health Science Network; AUC = area under the curve; DPIA = Data Protection Impact Assessment; ECG = electrocardiogram; EM = elctrocardiographic monitoring; ID = identification; IS = Istel; KM = KardiaMobile; NENC = North East and North Cumbria; NHMRC = National Health Medical Research Council; NR = not reported; QTc = corrected QT; SOP = standard operating procedure; TEWV = Tees Esk and Wear Valley; UK = United Kingdom; USA = United States of America

4.2 Study quality

Assessment of the methodological quality of included technical validation studies, based on QUADAS-2, indicted low or unclear risk of bias in all domains, for all studies. However, it should be noted that none of these studies was a diagnostic test accuracy study (the study type for which QUADAS-2 is intended to be used), in that none of them reported data about the ability of the index test (KardiaMobile 6L) to determine the presence or absence of a clinical condition or intermediate outcome (e.g., QTc prolongation at a clinically relevant threshold), as defined by the reference standard method (12-lead ECG).

Applicability to the decision problem under consideration was the major issue for all of the published studies included in this EVA report. Concerns regarding the applicability of these studies were high for both relevant domains (population and index test) were high for all studies.

Concerns regarding the applicability of study populations were high, for all studies, because no study was conducted in the population of interest for this EVA, i.e., service users requiring antipsychotic medication.

Concerns regarding the applicability of the index test were high because, in all studies, all ECGs were interpreted by cardiologists and in three[14, 40, 51] of the five studies assessed interpretation was undertaken by multiple readers. Measures of agreement with cardiologist-interpreted 12-lead ECG, where KardiaMobile 6L ECG results have been generated by multiple/expert readers, are unlikely to be reproducible by single non-cardiologist healthcare professionals, in real world settings.

The results of the QUADAS-2 assessment are summarised in Table 3 and the full assessments are provided in Appendix 2.

Two unpublished project reports have been included in this EVA report.[53, 54] These reports concern real world piloting of KardiaMobile 6L in two NHS Foundation Trusts (TEWV and CNTW), which was undertaken under considerable operational pressures during the COVID-19 pandemic. These reports do not describe formal research projects with *a priori* research objectives and methods designed to address these objectives; therefore, we did not consider formal assessment of methodological quality or risk of bias to be appropriate. The following text provides a qualitative summary of the key issues, with respect to the reliability of the information provided by these reports to address the aims of this EVA.

However, it is important to note that these reports concern pilot projects which were not designed to be used in wider evaluations of KardiaMobile 6L for use in the NHS, such as the current EVA.

Potential sampling bias

The two pilots involved the distribution of [redacted][53] and 40[54] KardiaMobile 6L devices across multiple locations. [redacted], there is a potential for bias in survey responses arising from inclusion of staff who may have an *a priori* positive view on the potential usefulness of KardiaMobile 6L devices.

Issues relating to the reporting of numbers and outcome measures

Both unpublished pilot project reports included sections on [redacted].[53, 54] [redacted].[53, 54] Where detail was provided (in addition to the yes/no response) this indicated that all changes reported were primarily in relation to service user care, with only one response making a subjective link to clinical outcome: *'Able to start antipsychotic medication quicker than usual, as patient would have had a delay in getting a regular ECG done, therefore able to begin treatment almost straightaway resulting in early resolution of psychotic symptoms, and early recovery.'*[54]

The CNTW end of project report indicated that 51 ECGs had been recorded, using KardiaMobile 6L devices during the pilot period.[54] However, the number 51 was recorded as the denominator for data taken from the survey of staff members who had used the KardiaMobile 6L devices.[54] Taken together with further information from an additional survey, which stated that (as of 30 September 2021) a total of 59 ECGs had been recorded using the KardiaMobile 6L devices and 16 staff indicated that they had used the devices,[54] this would indicate that the 51 survey responses included multiple responses per staff member. Whilst this would have been appropriate for questions (e.g., change to clinical

outcome) relating to per patient outcomes, it raises the potential problem of double counting with respect per staff member outcomes (e.g., staff preferences for KardiaMobile 6L or 12-lead ECG).[53, 54]

[redacted]

Potential bias in survey questions

The two unpublished pilot project reports did not include full copies of the survey instruments used to collect information from staff and service users;[53, 54] Word versions of the CNTW online surveys have been provided separately (see Appendix 5). From the questions that were presented, there was some indication that the choice of questions/wording may have introduced bias in favour of KardiaMobile 6L.[54] For example, rather than being asked their views about using KardiaMobile 6L with equal weight being given to advantages and disadvantages, staff were asked about *'benefits'* and *'least helpful aspects'*.[54] Similarly, when staff and service users were asked about their preferences (KardiaMobile 6L versus 12-lead ECG), the supplementary questions used to inform preferences all focussed on aspects of the ECG examination likely to favour the KardiaMobile device (ease of use, time savings, dignity and privacy, intrusiveness, comfort); no questions about clinical utility/reliability for decision making were reported.[54] It was unclear whether staff or service users were ever asked to consider, e.g. the extent to which a 'normal' ECG reading, by each method, could reliably indicate 'safety' to proceed with antipsychotic treatment.

Provision of information to staff members and service users using KardiaMobile 6L and completing the survey

The CNTW end of project summary report included links to online information and training materials that were provided to staff as part of the pilot.[54] Service users were given a choice of whether to have KardiaMobile 6L or 12-lead ECG and were directed to the AliveCor website for information about the device (verbal communication from Jonathan Richardson of CNTW to MW on 16 June 2022). When evaluating a new method of testing, such as KardiaMobile 6L, as part of a research project, the properties and intended use of the new method should be explained to study participants (staff and patients), e.g. that this is an initial test and any problems identified will be followed up with further testing and, importantly, what are the implications of a negative/normal test result (e.g. if 100 patients

were tested using the KardiaMobile 6L, X would have a negative/normal test result and Y of these would actually have a problem that would have been identified using 12-lead ECG). Based on the findings of our systematic review, the implications of a negative/normal test result could not have been provided, because no information about the clinical diagnostic accuracy of KardiaMobile 6L has been identified (for any population) However, it could therefore be argued that, if these data have not been collected before future observational before and after implementation research studies, participants should be advised (using appropriate methods of explanation) that the clinical accuracy of the device, and hence the risk of obtaining false reassurance from a negative/normal result, is unknown.

Collection of workflow information through staff survey

Information about the average number of ECGs undertaken per month and average time taken to complete an ECG examination (both KardiaMobile 6L and 12-lead ECG) were taken from a retrospective survey of staff.[54] It may be possible to obtain more reliable information about the number of ECGs currently undertaken per month from NHS Trust records or from observational studies (see Section 5.3). Information about the mean time taken to complete an ECG examination, by each method, should be obtained by direct measurement (either in the context of research studies or real world observations). In addition, there is a potential for bias in the estimates of average time taken to complete an ECG examination, in that only those staff who had chosen to use the KardiaMobile 6L device, during the pilot period, were asked to provide information about the average time taken to complete an examination (for both KardiaMobile 6L and 12-lead ECG).[54]

Estimation of costs

Both unpublished pilot project reports included estimates of cost per ECG and projected annual costs, for both KardiaMobile 6L and 12-lead ECG, as well as estimates of the projected annual cost savings associated with the introduction of KardiaMobile 6L.[53, 54] The methods used to obtain costs estimates, from the TEWV NHS Foundation Trust pilot, were not fully explained.[53] [redacted]. Importantly, the estimates presented for the KardiaMobile 6L testing pathway did not include the costs of subsequent 12-lead ECGs (whether required for follow-up of an abnormal finding or because of failure to obtain an adequate reading using KardiaMobile 6L), which were reported as being required at a rate of 60%.[54] Finally, acquisition costs were included for both devices;[54]

it is not clear whether this was appropriate as, if current practice is to attempt a 12-lead ECG in all cases, then sufficient 12-lead ECG devices should already be available to support this.

Table 3: QUADAS-2 results for technical validation studies of KardiaMobile 6L

Study ID	Risk of bias				Applicability concerns	
	Patient selection	Index test	Reference standard	Flow and timing	Study population	Index test
Azram 2021[14]	☺	☺	☺	?	☹	☹
Kleijman 2021[30]	?	☺	☺	☺	☹	☹
Krzowski 2021[51]	?	☺	☺	☺	☹	☹
Minguito-Carazo 2021[36]	?	?	?	?	☹	☹
Orchard 2021[40]	?	?	?	☺	☹	☹

☺ = Low Risk ☹ = High Risk ? = Unclear Risk

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

All eight of the published studies included in this report were either technical validation studies[14, 30, 36, 40, 51] or case series,[25, 41, 52] reporting some, very limited, information about the agreement between QT interval (corrected and/or uncorrected) measured by KardiaMobile 6L and QT interval (corrected and/or uncorrected) measured by standard 12-lead ECG. Details of study populations, ECG methods and interpretation are provided in Table 4 and the results of these studies are summarised in Table 5.

No study reported sufficient data to allow the calculation of measures of clinical diagnostic performance (e.g., sensitivity and specificity) for the target condition i.e., QTc prolongation; hence these studies cannot provide any indication of the proportion of patients, with QTc prolongation, who might be missed if KardiaMobile 6L were used for initial ECG assessment (triage). Where reported or calculable, the mean difference in QTc between devices (12-lead ECG versus KardiaMobile 6L) was generally small (≤ 10 ms), see Table 5. However, one study, which reported data for 605 patients who had been referred to a genetic heart rhythm clinic, reported that the absolute difference in QTcF (correction method used, Fridericia or Framingham, not reported in the paper), measured by 12-lead ECG and KardiaMobile 6L, was ≥10 ms in 56% of participants and ≥40 ms in 5% of participants.[30] In general, the direction of the difference between the two methods indicated that KardiaMobile 6L underestimated the QTc in comparison to the corresponding 12-lead QTc readout. However,

there was no information to indicate in how many (if any) patients this difference would have resulted in a change of clinical category.

With respect to failure rates, data were again very limited. One study reported a comparison, between KardiaMobile 6L and 12-lead ECG, with respect to the proportion of patients for whom each lead could be analysed (51 to 72% for KardiaMobile 6L and 55% to 77% for 12-lead ECG; the longest lead was usable for QTc in 80.4% of patients for 12-lead ECG and in 75.9% of patients for KardiaMobile 6L.[14] This study reports One further study reported that, for KardiaMobile 6L, QTc could be measured in lead II in most cases (90.9%).[36]

As described in Section 4.2, above, all of the included technical validation studies have very limited applicability to the clinical setting specified for this EVA.

Table 4: Study details for technical validation studies and case series

Study ID	Participants details n (%)	Details of index test (KardiaMobile 6L)	Details of comparator/reference standard (12-lead ECG)
Azram 2021 (EVALECG Cardio)[14]	**Cardiology patients:** 1,015 **Mean age ± sd (years):** 62 ± 17 **Male:** 634 (62.4) **Caucasian:** 767 (75.6) **South Asian:** 62 (6.1) **Black:** 14 (1.4) **Other:** 172 (16.9) **Diabetes:** 193 (19) **Hypertension:** 385 (37.9) **Previous coronary disease:** 278 (27.4) **History of arrhythmia:** 258 (25.4) **Known AF:** 207 (20.4) **Mean BMI ± sd:** 28.6 ± 9 **Outpatients:** 613 (60.4) **Inpatients:** 402 (39.6) **Indication for ECG** **Valve disease:** 116 (11.4) **Arrhythmia:** 116 (11.4) **Heart failure:** 262 (25.8) **Coronary disease:** 478 (47.1) **Inherited arrhythmia assessment:** 110 (10.8)	**Device settings:** Two handheld electrodes and a third electrode was placed on the left thigh (or the left ankle if this was not possible); maximum recording time programmed to 30 seconds (s); filter settings 0.05–40 Hz; sampling rate 300 /s; sweep speed of 25 mm/s; amplitude of 1 mm/mV. **Recording:** Stored as a PDF on a mobile phone and then printed onto plain paper. **Interpretation:** Three experienced observers (one cardiologist and two cardiac physiologists) performed the ECG analysis independently of each other. Each ECG was analysed twice.	**Device and settings:** MAC 550 (GE Healthcare, WI, USA); filter settings 0.05–100 Hz; sweep speed of 25 mm/s; amplitude of 1 mm/mV. **Recording:** Printed directly to ECG graph paper. **Interpretation:** Three experienced observers (one cardiologist and two cardiac physiologists) performed the ECG analysis independently of each other. Each ECG was analysed twice.
Frisch 2021[25]	**Hospitalised COVID-19 patients, requiring ECG monitoring:** 4	**Device settings:** NR **Recording:** Patients completed two	**Device and settings:** NR **Recording:** NR

	Age (years): 45; 48; 67; 96 **Comorbidities:** renal cancer (left nephrectomy and a renal transplant), hypertension, morbid obesity, and sleep apnoea; none; advanced systolic heart failure and persistent atrial fibrillation; atrial fibrillation treated with anticoagulation therapy, mild aortic stenosis, dyslipidemia, hypertension, chronic kidney disease, and anaemia. **Male:** 3 (75)	recordings using the KardiaMobile 6L device with the health care provider outside the room. After a successful recording, the cardiologist let the patient know that the recording had been completed. **Interpretation:** QT/QTc interval analysis was requested through the KardiaPro account. Once requested, the QT/QTc interval analysis was performed by BioTelemetry, Inc. (Malvern, PA, USA), an independent third-party QTc measuring service. Within one hour, a cardiologist logged on to the KardiaPro website to review the mECG, the automatic interpretation, and the QT/QTc interval measurements reported by the third-party source.	**Interpretation:** NR
Kleiman 2021[30]	**Patients referred to a Genetic Heart Rhythm Clinic between April 2018 and February 2020:** 705 (KardiaMobile 6L and 12-lead ECG results available for 685) **Mean age ± sd (years):** 28.7 ± 18.5 **Male:** 303 (43) **Diagnoses after comprehensive**	**Device settings:** Two hand held electrodes and a third electrode on the left leg; two minute recordings. **Recording:** Recordings taken by the patient. Using a smartphone-based application, the digital files containing the 6L recording were uploaded to a cloud-based server.	**Device and setting:** GE Marquette 12-lead ECG device; patients in the supine position; filtered at 500 Hz. **Recording:** ECGs from each subject were transferred digitally to a centralised ECG core laboratory, ERT, and were uploaded into ERT's validated data management system,

	cardiovascular evaluation **LQTS:** 343 (50) **Normal:** 146 (21) **Hypertrophic cardiomyopathy:** 36 (5.2) **Arrhythmogenic cardiomyopathy:** 23 (3.4) **Idiopathic ventricular fibrillation:** 14 (2.0)	ECGs from each subject were transferred digitally to a centralised ECG core laboratory, ERT, and were uploaded into ERT's validated data management system, EXPERT. IDMs were collected using computer-assisted calliper placements on three consecutive beats. **Interpretation:** ECGs were analysed by a cardiologist.	EXPERT. IDMs were collected using computer-assisted calliper placements on three consecutive beats. **Interpretation:** ECGs were analysed by a cardiologist.
Krzowski 2021[51]	**Consecutive inpatients in a tertiary care cardiology ward:** 98 **Mean age ± sd (years):** 69 ± 12.9 **Male:** 62 (63) **Smoking (current or former):** 47 (48) **Diabetes:** 40 (40.8) **Hypertension:** 72 (73.4) **Dyslipidaemia:** 72(73.4) **Chronic kidney disease:** 25 (25.5) **Thyroid dysfunction:** 19 (19.4) **Asthma:** 4 (4.1) **COPD:** 9 (9.2) **Stable angina:** 31(31.6) **ACS (admission):** 15 (15.3) **Previous MI:** 31 (31.6) **Previous PCI/CABG:** 41 (41.8)	**Device settings:** Two handheld electrodes and a third electrode on the left leg, no further details reported. **Recording:** Experienced technicians performed all recordings. **Interpretation:** All ECG recordings assessed by one of the two independent groups of experienced physicians. Every ECG was analysed by a younger cardiologist and checked by a senior physician; disagreements were resolved by discussion.	**Device and settings:** No details reported. **Recording:** Experienced technicians performed all recordings. **Interpretation:** All ECG recordings assessed by one of the two independent groups of experienced physicians. Every ECG was analysed by a younger cardiologist and checked by a senior physician; disagreements were resolved by discussion.

	Heart failure: 55 (56.1) **AF:** 43 (43.9) **CIED implanted:** 34 (34.7) **Pacemaker:** 22 (22.4)		
Minguito-Carazo 2021[36]	**Healthy (COVID-19 PCR negative) control patients:** 45 **Mean age ± sd (years):** 63.7 ± 18.1 **Male:** 26 (56.8) **No further details reported**	**Device settings:** The patient was told to sit and place the device on the bare skin of their left leg (at the knee or the ankle) holding his thumbs on the top of two electrodes for 30 s. **Recording:** The ECG registry was wirelessly transmitted to a and digitally uploaded by a dedicated app to a secure server. **Interpretation:** ECG records were reviewed and interpreted by at least one of two cardiologists. QTc interval was calculated using Bazett's formula in leads II or V5 in the 12-lead ECG and in lead II when using the handheld 6-lead ECG. If these leads did not provide an accurate end of the T wave, I and aVL were preferably used as an alternative, although QTc measurement in any other lead was permitted.	**Device and settings:** No details reported. **Recording:** No details reported. **Interpretation:** ECG records were reviewed and interpreted by at least one of two cardiologists. QTc interval was calculated using Bazett's formula in leads II or V5 in the 12-lead ECG and in lead II when using the handheld 6-lead ECG. If these leads did not provide an accurate end of the T wave, I and aVL were preferably used as an alternative, although QTc measurement in any other lead was permitted.
Orchard 2021[40]	**Healthy athletes with no existing cardiac**	**Device settings:** 30 s recording	**Device settings:** Recorded supine.

	diagnoses or family history of conditions associated with sudden cardiac death: 30 **Mean age ± sd (years):** 18.9 ± NR **Male: 17** (57) **No further details reported**	whilst seated. **Recording:** No details reported. **Interpretation:** ECGs were analysed by four expert cardiologists; manual measurements were taken for QT interval using EPS digital callipers; QTc was calculated using Bazett's formula.	**Recording:** No details reported. **Interpretation:** ECGs were analysed by four expert cardiologists; manual measurements were taken for QT interval using EPS digital callipers; QTc was calculated using Bazett's formula.
Puranik 2022[41]	**Patients with multidrug-resistant tuberculosis or non-tuberculous mycobacterium, who were receiving cardiotoxic medications:** 16 **No further details reported**	**Device settings:** No details reported. **Recording:** No details reported. **Interpretation:** QTc calculations used the Bazett's formula. Manually calculated QT intervals from lead II of the AliveCor tracing were analysed. Manual calculations involved counting the number of 1 mm squares from the start of the QRS complex to the end of the T wave – to calculate the QT interval - and using a standard formula (QTc = QT interval / √ (RR interval). Three clear areas of the AliveCor tracing were selected at random and an average of the QT interval was calculated.	**Device and settings:** Mortara ELI350; no further details reported. **Recording:** No details reported. **Interpretation:** QTc calculations used the Bazett's formula.

Shah 2021[52]	**Patients undergoing antiarrhythmic drug loading at home, during COVID-19 social distancing:** 3 **Participant 1:** 35-year-old woman, hypertrophic cardiomyopathy, ejection fraction 35%, symptomatic paroxysmal AF **Participant 2:** 40-year-old man, alpha-actinin-2 deletion, history of ventricular fibrillation, sinus bradycardia, and symptomatic paroxysmal AF **Participant 3:** 60-year-old man, hypertrophic cardiomyopathy, symptomatic ventricular tachycardia episodes refractory to sotalol	**Device settings:** No details reported. **Recording:** No details reported. **Interpretation:** No details reported.	**Device and setting:** No details reported. **Recording:** No details reported. **Interpretation:** No details reported.

6L = 6-lead; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CIED = cardiovascular implantable electronic device; ECG = electrocardiogram; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; ERT = eResearch Technology; Hz = Hertz; IDM = interval duration measurement; LQTS = long QT syndrome; mECG = multilead electrocardiogram; MI = myocardial infarction; mm = millimetre; mV = millivolt; NR = not reported; PCI = percutaneous coronary intervention; PCR = polymerase chain reaction; PDF = portable document format; s = seconds; sd = standard deviation; USA = United States of America

Table 5: Summary of results from technical validation studies and case series

Study ID	Number (%) ECGs analysed, by KardiaMobile	Number (%) ECGs analysed, by 12-lead	Mean or median QT interval, by KardiaMobile 6L (ms)	Mean or median QT interval, by 12-lead ECG (ms)	Difference/concordance measure	Other outcomes
Azram 2021 (EVALECG Cardio)[14]	**QT** **Lead I:** NR (71.6)	**QT** **Lead I:** NR (67.9)	NR	NR	**Mean difference (LLA, ULA) (ms), 12-lead versus KardiaMobile 6L**	**Proportion of patients where QTc[a] analysis was possible (by lead)**

	Lead II: NR (72.8) **Lead III:** NR (51.4) **Lead AVR:** NR (71.9) **Lead AVL:** NR (66.1) **Lead AVF:** NR (57.0) **Longest:** NR (75.9) **QTc**[a] **Lead I:** NR (71.5) **Lead II:** NR (72.8) **Lead III:** NR (51.3) **Lead AVR:** NR (71.8) **Lead AVL:** NR (66.0) **Lead AVF:** NR (56.9) **Longest:** NR (75.9)	**Lead II:** NR (76.6) **Lead III:** NR (55.4) **Lead AVR:** NR (68.6) **Lead AVL:** NR (58.2) **Lead AVF:** NR (61.5) **Longest:** NR (80.4) **QTc**[a] **Lead I:** NR (67.9) **Lead II:** NR (76.6) **Lead III:** NR (55.4) **Lead AVR:** NR (68.6) **Lead AVL:** NR (58.2) **Lead AVF:** NR (61.5) **Longest:** NR (80.4)			**QT** **Lead I:** 6.29 (-36.21, 48.79) **Lead II:** 7.03 (-31.80, 45.87) **Lead III:** 6.47 (-40.54, 53.48) **Lead AVR:** 7.06 (-34.46, 48.57) **Lead AVL:** 5.45 (-38.65, 49.56) **Lead AVF:** 8.49 (-36.59, 53.57) **Longest QT interval:** 11.6 (-28.79, 52.31) **QTc**[a] **Lead I:** -0.27 (-55.48, 54.93) **Lead II:** 0.62 (-51.95, 53.19) **Lead III:** 1.15 (-55.05, 57.35) **Lead AVR:** -0.03 (-53.15, 53.10) **Lead AVL:** -2.02 (-57.65, 53.61) **Lead AVF:** 2.35 (-54.76, 59.46) **Longest QTc interval:** 5.71 (-47.42, 58.85)	**Lead I:** 12-lead ECG 67.9%; KardiaMobile 6L 71.5% **Lead II:** 12-lead ECG 76.6%; KardiaMobile 6L 72.8% **Lead III:** 12-lead ECG 55.4%; KardiaMobile 6L 51.3% **Lead AVR:** 12-lead ECG 68.6%; KardiaMobile 6L 71.8% **Lead AVL:** 12-lead ECG 58.2%; KardiaMobile 6L 66.0% **Lead AVF:** 12-lead ECG 61.5%; KardiaMobile 6L 56.9% **Longest QTc**[a] **lead:** 12-ECG 80.4%; KardiaMobile 6L 75.9% **AUC** AUC, where a normal QT interval was defined as 360 to 460 ms: QT >70% (80% for the best lead); QTc >60% (74% for the best lead).
Frisch 2021[25]	**QT**	**QT**	**Mean ± sd**	**Mean ± sd**	**Mean difference (95% CI) (ms), 12-lead**	All patients were able to

	7 (87.5) **QTc**[b] 7 (87.5)	8 (100) **QTc**[b] 8 (100)	**QT** 365 ± 25[c] **QTc**[b] 460 ± 30[c]	**QT** 366 ± 15[c] **QTc**[b] 464 ± 19[c]	**versus KardiaMobile 6L** **QT** 1.00 (-20.24, 22.24)[c] **QTc**[b] 4.00 (-21.83, 29.83)[c]	record KardiaMobile 6L ECGs independently.
Kleiman 2021[30]	**QT** 671 (95.2) **QTcF**[d] 674 (95.6)	**QT** 674 (95.6) **QTcF**[d] 674 (95.6)	**Mean ± sd** **QT** 407.5 ± 49.14 **QTcF**[d] 428.5 ± 36.50 **Median (min, max)** **QT** 405 (490, 792) **QTcF**[d] 427 (327, 746)	**Mean ± sd** **QT** 420.9 ± 51.87 **QTcF**[d] 431.0 ± 38.80 **Median (min, max)** **QT** 419 (306, 791) **QTcF**[d] 427 (316, 744)	**Mean difference (95% CI) (ms), 12-lead versus KardiaMobile 6L** **QT** 13.40 (8.00, 18.80) **QTcF**[d] 2.50 (-1.52, 6.52) **Categorical breakdown of difference in QTcF**[d] **between 6L and 12-lead, n (%)** **Absolute difference <10:** 297(44.3) **Absolute difference 10 to 19:** 221 (32.9) **Absolute difference 20 to 29:** 69 (10.3) **Absolute difference 30 to 39:** 50 (7.5) **Absolute difference 40 to 49:** 19 (2.8) **Absolute difference ≥ 50:** 15 (2.2)	Patients reported no difficulties in recording ECGs using the KardiaMobile 6L device. All 12-lead ECGs were of sufficient quality to allow IDM measurements and cardiologist interpretation, and only one of the 6L ECGs was unsuitable for IDM measurements (excessive artifact) but was adequate for cardiologist interpretation.
Krzowski 2021[51]	97 (99)	98 (100)	**Mean ± sd** **QT** 366 ± NR	**Mean ± sd** **QT** 403 ± NR	**Not calculable**	**ECG quality ratings, n (%)** **KardiaMobile 6L** **Good:** 70 (72) **Acceptable:** 22 (23)

						Poor: 5 (5) **12-lead ECG** **Good:** 80 (82) **Acceptable:** 17 (17) **Poor:** 1 (1)
Minguito-Carazo 2021[36]	45 (100)	45 (100)	**Mean ± sd** **QTc**[a] 409.1 ± 23.2	**Mean ± sd** **QTc**[a] 411.8 ± 25.7	**Mean difference (95% CI) (ms), 12-lead versus KardiaMobile 6L** **QTc**[a] 2.7 (-7.7, 23.2)	For KardiaMobile 6L, QTc could be measured in lead II in most cases (90.9%)
Orchard 2021[40]	30 (100)	30 (100)	**Mean ± sd** **QT** 363 ± 28 **QTc**[a] 391 ± 24	**Mean ± sd** **QT** 381 ± 26 **QTc**[a] 401 ± 25	**Mean difference (95% CI) (ms), 12-lead versus KardiaMobile 6L** **QT** 18.0 (4.33, 31.67)[c] **QTc**[a] 10.0 (-2.40, 22.40) [c]	None
Puranik 2022[41]	13 (81.3)	13 (81.3)	NR	NR	The mean percentage difference between the automated 12-lead and manually calculated KardiaMobile 6L readings was 3%. The largest percentage difference between the two readings was 12%.	In 12/13 cases (92%), KardiaMobile 6L underestimated the QTc in comparison to the corresponding 12-lead QTc readout. Pearson's correlation coefficient = 0.43.

Shah 2021[52]	3 (100)	3 (100)	**QTc**[b] **Pre-loading** **Participant 1:** 423 **Participant 2:** 417 **Participant 3:** 430 **Post-loading** **Participant 1:** 430 **Participant 2:** 421 **Participant 3:** 451	**QTc**[b] **Pre-loading** **Participant 1:** 420 **Participant 2:** 419 **Participant 3:** 422 **Post-loading** **Participant 1:** 439 **Participant 2:** 415 **Participant 3:** 459	**Difference (ms) QTc**[b]**, 12-lead versus KardiaMobile 6L** **Pre-loading** **Participant 1:** -3 **Participant 2:** 2 **Participant 3:** -8 **Post-loading** **Participant 1:** 9 **Participant 2:** -6 **Participant 3:** 8	Initially, participants described less than maximal (≤7/10) perceived ease using the KardiaMobile 6L, however, by study completion all reported the highest level of comfort with operating the device and transmitting ECGs.

[a]Calculated using Bazett's formula
[b]Correction method not reported
[c]Calculated value
[d]The correction method used (Fridericia or Framingham) was not reported in the paper
6L = 6-lead; AUC = area under the curve; AVF = augmented vector foot; AVL = augmented vector left; AVR = augmented vector right; CI = confidence interval; ECG = electrocardiogram; IDM = interval duration measurement; max = maximum; min = minimum; ms = milliseconds; NR = not reported; sd = standard deviation

4.4 What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?

We did not identify any studies which assessed the clinical effects of implementing KardiaMobile 6L ECG. All information in this Section has been taken from unpublished project reports.[53, 54]

It is important to note that both of these projects relate to work undertaken as part of a wider AHSN pilot, they were not formal research projects and were not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

Both the unpublished pilot project reports provided [redacted] [53, 54] Responses were per staff member and not (as would be expected for change to clinical outcome) per patient.

The end of project summary report, from CNTW NHS Foundation Trust,[54] reported responses to this question from six healthcare professionals; two responses indicated that the use of KardiaMobile 6L facilitated commencement of antipsychotic medication, two responses indicated that the KardiaMobile 6L result had been used to rule out heart abnormalities, and indicated that a 12-lead ECG was still needed. Only one of the six responses linked the change in care reported to clinical outcome: *'Able to start antipsychotic medication quicker than usual, as patient would have had a delay in getting a regular ECG done, therefore able to begin treatment almost straightaway resulting in early resolution of psychotic symptoms, and early recovery.'*[54] The number of ECGs/patients to which these observations applied was not clear.

[redacted]

It should be noted that (with the exception of one response) all of the information, recorded in the two unpublished pilot project reports,[53, 54] [redacted]

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

One technical validation study[36] reported a comparison of the time taken to record an ECG with KardiaMobile 6L versus 12-lead ECG; based on ECGs of 45 patients taken by both methods. The mean time taken to record a 12-lead ECG was slightly longer than that taken to record an ECG using KardiaMobile 6L (mean difference 2.1 (95% confidence interval [CI]: 1.9, 2.3) minutes). Although it did not meet the inclusion criteria for this question, because it was not conducted in service users requiring antipsychotic medication, data from this study have been included in this section, for completeness.[36]

The remaining information in this Section has been taken from unpublished project reports.[53, 54]
It is important to note that both of these project reports relate to work undertaken as part of a wider AHSN pilot, they were not formal research projects and were not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

Both of the unpublished pilot projects[53, 54] [redacted] and 19 minutes, respectively); [redacted] In the case of the CNTW report[54] the estimate of time saved was based on categorical information from a retrospective survey of those healthcare professionals who had used the KardiaMobile 6L device. In that survey, staff were asked, '*Approximately, and on average, how long would you spend with each patient when carrying out a usual ECG?'* and '*Approximately, and on average, how long have you spent with each patient when carrying out a ECG with the KardiaMobile 6L (app & device)?'* and response options were *'less than 5 mins'*, *'5-10 mins'*, *'11-20 mins'*, *'21-31 mins'*, *'32+ mins'* and *'other'*.[54] The estimate of average time taken was reported to have been based on the average of each time option available and frequency of reporting.[54] [redacted][53]

Both of the unpublished pilot projects[53, 54] reported [redacted] In the CNTW end of project report, nine of the 16

healthcare professionals (56%), who stated that they had used the KardiaMobile 6L device, answered *'yes'* to the question *'Did the clinical situation require subsequent use of a 12-lead ECG after using the AliveCor KardiaMobile 6L device?'* As with the TEWV pilot, it was not clear as to how many ECGs/service users the reported requirement for an additional 12-lead ECG applied; specific reasons given for the additional 12-lead ECG requirement were poor readings (e.g. due to patient movement or inability to maintain contact with the electrodes) in four instances, requirement for more information or follow-up monitoring in three instances, and an abnormal result in one instance.[54]

Regarding the preferences/satisfaction of service users and healthcare professions, [redacted][53] The survey of healthcare professionals, reported in the CNTW end of project report,[54] asked participants to indicate their preference for KardiaMobile 6L or 12-lead ECG with respect to five characteristics and to indicate an overall preference; 48/51 (94.1%) respondents indicated a preference for KardiaMobile 6L with respect to ease of use, 50/51 (98%) preferred KardiaMobile 6L for dignity and privacy, 44/51 (86.2%) indicated that they considered 12-lead ECG to be the more intrusive option, 49/51 (96%) indicated that they considered KardiaMobile 6L to be the more comfortable option, 40/51 (78.4%) indicated a preference for KardiaMobile 6L with respect to ease of sending information to the relevant professional, and 42/51 (82.3%) indicated an overall preference for KardiaMobile 6L.[54] A similar survey was reported for service users, 33 of whom provided responses; 32/33 (96.9%) indicated a preference for KardiaMobile 6L with respect to ease of use and dignity and privacy, 32/33 (96.9%) indicated that they considered 12-lead ECG to be the more intrusive option, all 33 (100%) indicated that they considered KardiaMobile 6L to be the more comfortable option, 31/33 (93.9%) indicated an overall preference for KardiaMobile 6L, and 32/33 (96.9%) indicated that they would prefer KardiaMobile 6L for future monitoring.[54]

Table 6: Details of studies reporting information on service user acceptability/satisfaction and on training and workflow issues

Study ID	Participants details n (%)	Details of index test (KardiaMobile 6L)	Details of comparator/reference standard (12-lead ECG)
Minguito-Carazo 2021[36]	**Healthy (COVID-19 PCR negative) control patients:** 45 **Mean age ± sd (years):** 63.7 ± 18.1 **Male:** 26 (56.8) **No further details reported**	**Device settings:** The patient was told to sit and place the device on the bare skin of his left leg (at the knee or the ankle) holding his thumbs on the top of two electrodes for 30 seconds (s). **Recording:** The ECG registry was wirelessly transmitted to a and digitally uploaded by a dedicated application to a secure server. **Interpretation:** ECG records were reviewed and interpreted by at least one of two cardiologists. QTc interval was calculated using Bazett's formula in leads II or V5 in the 12-lead ECG and in lead II when using the handheld 6L ECG. If these leads did not provide an accurate end of the T wave, I and aVL were preferably used as an alternative, although QTc measurement in any other lead was permitted.	**Device and settings:** No details reported. **Recording:** No details reported. **Interpretation:** ECG records were reviewed and interpreted by at least one of two cardiologists. QTc interval was calculated using Bazett's formula in leads II or V5 in the 12-lead ECG and in lead II when using the handheld 6L ECG. If these leads did not provide an accurate end of the T wave, I and aVL were preferably used as an alternative, although QTc measurement in any other lead was permitted.
Tees and Esk and Wear Valleys NHS Foundation Trust 2021[53]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	
Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust 2021[54]	Not explicitly stated, but appears to have been service users in whom ECG was indicated in relation to the use of antipsychotic medication 40 KardiaMobile 6L devices were distributed across four regional localities; the end of project report indicated that, of 50 ECGs carried out using KardiaMobile 6L, 34 were conducted in the community and 16 in inpatient settings. No details were provided about the service users who received ECG assessment using KardiaMobile 6L.	**Device settings:** No details reported. **Recording:** No details were reported about the type of healthcare profession who recorded the ECG or their experience of recording ECGs. **Interpretation:** No details were reported about the type of healthcare profession who interpreted the ECG results or their experience of interpreting ECGs.	**Device and settings:** No details reported. **Recording:** No details reported. **Interpretation:** No details reported.
6L = 6-lead; ECG = electrocardiogram; NHS = National Health Service; PCR = polymerase chain reaction; s = seconds; sd = standard deviation			

Table 7: Comparison of time taken to obtain an ECG using KardiaMobile 6L and using 12-lead ECG

Study ID	Number (n) ECGs: healthcare professionals	Time to record ECG, by KardiaMobile 6L	Time to record ECG, by 12-lead ECG	Difference
Minguito-Carazo 2021[36]	45: NR	**Mean ± sd (s)** 93.3 ± 29.7	**Mean ± sd (s)** 217.8 ± 34.3	**Mean difference (s) (95% CI) (s), 12-lead versus KardiaMobile 6L:** 124.5 (111.4, 137.6)[a]
Tees and Esk and Wear Valleys NHS Foundation Trust 2021[53]	[redacted]	[redacted]	[redacted]	[redacted]
Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust 2021[54]	Unclear: Unclear The end of project report stated that a total of 50 ECGs had been recorded using KardiaMobile 6L (as of 31 August 2021). However, n= 51 was also variously reported as the number of healthcare workers and the number of teams who had used the device	**Estimated mean, based on categorical data from a retrospective survey of healthcare professionals, who were asked** '***Approximately, and on average, how long would you spend with each patient when carrying out an ECG with KardiaMobile 6L?'*** **Excluding travel time:** 8 mins 28 s **Including travel time:** 23 mins 35 s	**Estimated mean, based on categorical data from a retrospective survey of healthcare professionals, who were asked** '***Approximately, and on average, how long would you spend with each patient when carrying out a usual ECG?'*** **Excluding travel time:** 24 mins 28 s **Including travel time:** 44 mins 40 s	**Average time saved, using KardiaMobile 6L:** 19 mins

6L = 6-lead; CI = confidence interval; ECG = electrocardiogram; mins = minutes; NR = not reported; s = seconds;

4.6 What are the costs, from a UK NHS and PPS 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?

We did not identify any studies that reported information about the costs 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, either from a UK NHS and PSS perspective or in non-UK settings. All information on costs, included in this report, was derived from the two unpublished pilot project reports from TEWV and CNTW NHS Foundation Trusts.[53, 54]

It is important to note that both of these project reports relate to work undertaken as part of a wider AHSN pilot, they were not formal research projects and were not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

A presentation of the TEWV NHS Foundation Trust pilot[55] [redacted]

The end of project report from CNTW NHS Foundation Trust[54] included details of the costs associated with local interpretation of ECGS (by a '*doctor in training/CNTW member of staff'*) or interpretation by a centralised service. The report concluded that KardiaMobile 6L ECG was associated with a reduction in cost of £2.37, for a Band 3 member of staff to take the ECG reading, compared to 12-lead ECG. Although not explicitly stated, this estimate appeared to be based on an average reduction in staff time needed to take the ECG reading calculated from staff estimates provided in a retrospective survey (see Section 4.5). The report also provided the following estimates of total annual costs for 204 ECGs (workload estimate based on 51 ECGs conducted during the 3-month pilot period):

- KardiaMobile 6L = £1, 542.19 – based on ECG readings taken by a Band 3 staff member and local manual interpretation by a doctor in training/CNTW staff member, and including device costs (including iPad and licences)
- 12-lead ECG = £4,762.80 – based on ECG readings taken by a Band 3 staff member and local manual interpretation by a doctor in training/CNTW staff member, and including device costs (details not specified)
- 12-lead ECG = £8,779.56 – based on ECG readings taken by a Band 3 staff member and ECG being sent to a central location for immediate interpretation, and including device costs (details not specified)

Details of the comparative costs provided in the CNTW NHS Foundation Trust report[54] are provided in Table 8. Based on these estimates, the expected annual cost saving associated with using KardiaMobile 6L would be between £3,220.61 (based on ECGs, 6L and 12-lead were interpreted locally) and £7,237.27 (based on all 6L ECGs being interpreted locally and all 12-lead ECGs being interpreted immediately, using the centralised service). However, these estimates do not include the costs of any 12-lead ECG which are required following an initial ECG reading using KardiaMobile 6L (whether for clinical follow-up of an abnormal result or due to failure to record an adequate ECG using KardiaMobile 6L). The survey of staff, included in the CNTW NHS Foundation Trust report[54] found that 60% of respondents reported still requiring a 12-lead ECG after initial use of KardiaMobile 6L. Based on the estimate of 204 ECGs performed per year, 122 12-lead ECGs would be required in addition to the initial ECGs using KardiaMobile. Estimated annual costs, after the introduction of KardiaMobile 6L, including the requirement for 12-lead ECG in 60% of cases have been added to Table 8 (entries in red text); these estimates include costs of reading and interpreting a KardiaMobile 6L ECG in all cases (n=204), plus the costs of reading and interpreting a 12-lead ECG in 60% of cases (n=122), plus the device acquisition costs for both KardiaMobile 6L and 12-lead ECG.

It should be noted that all of the estimates for cost savings, derived from the total costs indicated in the CNTW NHS Foundation Trust report,[54] are substantially lower than the estimate for annual cost savings reported for the TEWV pilot.[55] Furthermore, when the costs of conducting additional 12-lead ECGs (at a rate of 60%) were taken into account, the figures in CNTW NHS Foundation Trust report,[54] indicate that introduction of KardiaMobile 6L could actually be associated with an increase in overall annual costs of £1,074.79 61 (based on ECGs, 6L and 12-lead being interpreted locally) or a reduction in overall annual costs of between £125.61 and £699.61 (based on all 6L ECGs being interpreted locally and all 12-lead ECGs being interpreted centrally).

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

We did not identify any cost effectiveness studies concerning QT interval assessment (by any ECG method), either prior to initiation of treatment or for monitoring during treatment, for service users who require antipsychotic medication.

Table 8: Comparison of annual ECG costs using KardiaMobile 6L versus 12-Lead device

ECG Type	Cost/ECG reading (Band 3 staff member)	Cost/ECG interpretation (local by doctor in training/CNTW staff member)	Cost/ECG interpretation (centralised service, immediate interpretation)	Cost/ECG interpretation (centralised service, overnight interpretation)	Cost/ECG interpretation (centralised service, weekend interpretation)	Total annual cost for 204 ECGs	Device set up costs	Total annual costs including device set up
KardiaMobile 6L	£1.52	£1.31	NA	NA	NA	£577.32	£964.87	£1,542.19
KardiaMobile 6L +12-lead ECG (applied to 122 [60%][a] of ECGs)	£5.91	£2.62				£1,272.72	£4,564.87	£5,837.59
	£5.91	£1.31	£21.00			£3,515.08	£4,564.87	£8,079.95
	£5.91	£1.31		£17.00		£3,027.08	£4,564.87	£7,591.95
	£5.91	£1.31			£14.00	£2,661.08	£4,564.87	£7,225.95
12-lead ECG	£4.39	£1.31				£1,162.80	£3,600.00	£4,762.80
	£4.39		£21.00			£5,179.56	£3,600.00	£8,779.56
	£4.39			£17.00		£4,363.56	£3,600.00	£7,963.56
	£4.39				£14.00	£3,751.56	£3,600.00	£7,351.56

[a]It should be noted that this rate was reported per staff member/survey respondent, and it was not clear to how many ECGs/service users it applied
CNTW = Cumbria, Northumberland and Tyne and Wear; ECG = electrocardiogram' NA = not applicable

5. DISCUSSION

5.1 Statement of principal findings

The evidence to inform this EVA of KardiaMobile 6L, for use in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication, was extremely limited.

We did not identify any studies, which addressed any of the five research questions defined for this EVA, in the target population (service users who require antipsychotic medication).

All eight of the research studies identified were technical validation studies[14, 30, 36, 40, 51] or case series,[25, 41, 52] reporting some, very limited, information relevant to research question 1, *'What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?'* All of these studies were conducted in non-psychiatric populations (e.g. cardiac patients, COVID-19 patients), and all used cardiologists to interpret all ECGs and, in some instances, also applied optimised methods of interpreting ECGs (multiple reader assessment),[14, 40, 51] such that the results obtained are unlikely to be reproducible by single non-cardiologist healthcare professionals, in real world settings. Where reported or calculable, the mean difference in QTc between devices (12-lead ECG versus KardiaMobile 6L), derived from these studies, was generally small (≤10 ms). However, the apparent direction of the difference between the two methods indicated that KardiaMobile 6L consistently underestimated the QTc in comparison to the corresponding 12-lead-derived value. Possible systematic underestimation of QTc may be a cause for concern, given that the intermediate outcome measure/target condition specified for this EVA was QT prolongation. However, it should be noted that none of the included studies provided any information to indicate in how many (if any) patients observed differences in measured QTc would have resulted in a change of clinical category.

All of the information about the use of KardiaMobile 6L in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication, included in this EVA report, was taken from two unpublished pilot project reports.[53, 54] These reports describe real world pilots of KardiaMobile 6L in two NHS foundation Trusts (TEWV and CNTW), which were funded by NHSX, via the AHSN NENC. They do not describe formal research projects and, as such, do not report *a priori* research objectives and methods designed to address these objectives. [redacted]

It is important to note that both of these project reports relate to work undertaken as part of a wider AHSN pilot, which was not intended to be used in wider evaluations of KardiaMobile 6L for use in the NHS.

The unpublished pilot project reports both [redacted] [53, 54] [redacted] Where additional detail was provided in support of the yes/no response, most respondents indicated that they were reporting a change to service user care rather than a change to clinical outcome; only one respondent linked the change in care reported to clinical outcome: *'Able to start antipsychotic medication quicker than usual, as patient would have had a delay in getting a regular ECG done, therefore able to begin treatment almost straightaway resulting in early resolution of psychotic symptoms, and early recovery.'*[54]

Both of the unpublished pilot project reports,[53, 54] [redacted] and 19 minutes, respectively). [redacted] [53] and nine of the 16 healthcare professionals (56%) in the CNTW NHS Foundation Trust end of project report,[54] who had used the KardiaMobile 6L device, reported that a subsequent 12-lead ECG was required; it was not clear to how many ECGs/service users the reported requirement for an additional 12-lead ECG applied.

Regarding the preferences/satisfaction of service users and healthcare professions, [redacted].[53] The results of the survey, reported in the CNTW NHS Foundation Trust end of project report,[54] indicated that 42/51 (82%) staff respondents and 31/33 (94%) service user respondents had an overall preference for KardiaMobile 6L over 12-lead ECG.[54]

A presentation of the TEWV NHS Foundation Trust pilot[55] [redacted] The CNTW NHS Foundation Trust end of project report[54] estimated that the expected annual cost saving associated with using KardiaMobile 6L would be between £3,220.61 and £7,237.27. However, these estimates did not include the costs of any 12-lead ECG required following an initial ECG reading using KardiaMobile 6L (whether for clinical follow-up of an abnormal result or due to failure to record an adequate ECG using KardiaMobile 6L). The

survey of staff, included in the CNTW NHS Foundation Trust end of project report[54] indicated 60% of respondents stated that a 12-lead ECG was still required after initial ECG using KardiaMobile 6L. Including the costs of an follow-up 12-lead ECG, at a rate of 60%, results in a maximum estimated annual cost saving of £699.61 and a possible annual cost increase of up to £1,074.79 61 associated with using KardiaMobile 6L. It should be noted that the rate of 60% was reported per staff member/survey respondent and it was not clear as to how many ECGs/service users it applied. Hence, the cost savings for KardiaMobile 6L, reported in the unpublished pilot project reports,[53, 54] are likely to be overestimates (because they did not include the costs of any follow-up 12-lead ECGs required) and the corrected values that we have calculated are likely to underestimate potential savings (because they involved applying a rate of follow-up 12-lead ECGs that had been reported per staff member rather than per ECG).

5.2 Strengths and limitations of assessment

This report describes the results of a novel process which is being developed to provide EVA of new diagnostic technologies, where the evidence base is, as yet, underdeveloped. This process is intended to be applied where topic scoping has indicated that there is not sufficient evidence to inform a full Diagnostic Assessment Report and to support the development of a cost effectiveness model(s). The use of an EVA approach acknowledges that there is currently not sufficient evidence to inform decision making about routine use in UK NHS clinical practice. The aim of the process, as implemented in this assessment, was to assess whether a new diagnostic technology has shown sufficient evidence of potential advantage(s) over current practice to justify further research to inform full assessment of its clinical and cost effectiveness and inform decision making, and to provide detailed recommendations about the research needed to inform such assessments.

The decision problem, for this assessment, was defined using the same process of scoping, expert and public consultation, and iterative drafting that would be used for a full Diagnostic Assessment; the decision problem, defined by this process, has informed our recommendations for research needed to inform a full Diagnostic Assessment (Section 6.2). The inclusion criteria defined for this EVA (see Section 3.2) were wider than would be indicated by the definition of the decision problem, for example, studies conducted in populations other than that specified (service users requiring antipsychotic medications) were included. This wider approach to inclusion provided the potential to identify and summarise studies which, whilst not directly applicable to the decision problem, may inform assessment of the potential of the test to be an effective and cost effective intervention. For example, if diagnostic accuracy studies had been identified which reported high sensitivity values for KardiaMobile 6L for the detection of QTc prolongation, when used by expert cardiologists in cardiology patients, this may have been considered sufficient indication of ‘good’ clinical diagnostic

performance to justify further research to assess whether clinical diagnostic performance could be maintained when the device is used in context specified by the decision problem. Similarly, evidence indicating benefits for KardiaMobile 6L in relation to secondary outcome measures, such as service user acceptability/preference, time taken to conduct an ECG or costs, which are not sufficient to inform decision making about routine use in UK NHS clinical practice (in the absence of higher-level outcomes data about the clinical efficacy and safety of the device), may be considered indicative of potential benefits, such that further research to assess clinical efficacy and safety is warranted.

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[56] search strategies were developed to maximise sensitivity at the expense of reduced specificity. In order to be as inclusive as possible we also conducted a search of the medRxiv the preprint server and asked clinical experts (specialist committee members for this topic) to provide details of any potentially relevant ongoing or unpublished studies, of which they were aware. Based on the submissions provided by the company (AliveCor) and clinical experts, we handsearched the journal, *European Heart Journal - Digital Health*, which is not yet indexed in the bibliographic databases searched. Thus, large numbers of citations were identified and screened, relatively few of which met the inclusion criteria of the review.

The following text describes the key limitations of the evidence identified, with respect to informing the aims of an EVA.

All of the evidence identified in relation to research question 1, *'What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?'* was obtained from studies conducted in non-psychiatric populations (e.g., cardiac patients, COVID-19 patients), and concerned the technical validation of the KardiaMobile 6L device only. Studies reported measures of agreement, for QT interval (corrected and/or uncorrected), between KardiaMobile 6L and 12-lead ECG, but did not provide data to assess the sensitivity and specificity of the device for the detection of clinically relevant QTc prolongation (clinical diagnostic accuracy). It is therefore not known to what, if any, extent the levels of disagreement observed between the KardiaMobile 6L and 12-lead ECG would result in patients with clinically relevant QTc prolongation being missed if KardiaMobile 6L were used for additional assessment. In addition, the methods/personnel used to interpret ECGs, in the

included technical validation studies, [14, 30, 36, 40, 51] were such that the results obtained are unlikely to be reproducible in the real world settings indicated by the decision problem.

All of the evidence, in relation to research questions 2 to 4, which concerns the use of KardiaMobile 6L in the population specified by the decision problem (service users who require antipsychotic medication), was derived from the results of surveys of staff and service users undertaken following pilots of the device in TEWV NHS Foundation Trust and CNTW NHS Foundation Trust.[53, 54] The reported survey findings provided some indication that the KardiaMobile 6L device was preferred, by both staff and service users, over 12-lead ECG and may also be associated with reductions in the time taken to obtain an ECG and in costs of obtaining an ECG. However, it should be noted that these surveys were not undertaken as formal research projects with *a priori* research objectives and, as such, they were subject to a large number of substantial limitations, both in respect of the methods used (e.g. potential sampling bias in that participants appear to have been included on the bases of their willingness to use KardiaMobile 6L, and potential question bias in that some survey questions appear to have been phrased in a way which would be likely to favour KardiaMobile 6L) and the information collected (e.g. some per patient/ECG outcomes, such as change to clinical management, were collected per participating staff member, and some easily measurable outcomes, such as time taken to obtain an ECG, were estimated from staff opinion). These limitations are described more fully in Section 4.2 of this report.

5.3 Uncertainties

Evidence to inform the aims of an EVA

With respect to test performance, we did not identify any evidence to support the technical validation of the KardiaMobile 6L device in the context specified by the decision problem, i.e., there were no studies which assessed the agreement between QT interval (corrected or uncorrected) determined using KardiaMobile 6L versus 12-lead ECG, when KardiaMobile 6L was used by the relevant healthcare professionals to assess service users who require antipsychotic medication. The methods/personnel used to interpret ECGs, in the included technical validation studies,[14, 30, 36, 40, 51] were such that the results obtained are unlikely to be reproducible in the real world settings indicated by the decision problem. In addition, no studies were identified which reported sufficient information to support estimation of measures of the clinical diagnostic performance of KardiaMobile 6L to identify the intermediate outcome/target condition QTc prolongation (in any population or setting). Hence there is currently no information to inform estimates of the potential clinical sensitivity/rule-out reliability of the device (in any population or setting) and to assess whether evaluation in the specified population (service users who require antipsychotic medication) is warranted. Although included studies reported some limited information about the proportion of

leads in which QT interval could be measured,[14] noted that all patients were able to independently record an ECG using KardiaMobile 6L,[25, 30] or reported subjective quality ratings,[51] (see Table 5), there were insufficient data to adequately assess the technical failure rates of KardiaMobile 6L when used to assess QT interval, particularly when used in the context of the assessment of service users who require antipsychotic medication. Qualitative staff survey information[54] indicated that manual calculation of QTc and confidence about doing this was a key area of concern for staff, and affected the willingness of some staff to use the device; this issue was emphasised, by CNTW project leads, as key for the potential implementation of the device (verbal communication from Jonathan Richardson, Stewart Little, Nicola Orkney of CNTW to MW on 16/06/2022).

The information provided in unpublished pilot project reports, under the heading [redacted] [53, 54] was very limited, did not allow for the estimation of per patient outcomes, and mainly referred to changes in care rather than changes in clinical outcome. Neither of the two project reports included any information about baseline (pre-piloting of KardiaMobile 6L) rates of adverse cardiac outcomes (arrhythmias, sudden cardiac death) or psychiatric outcomes (e.g. symptom duration, inpatient admission, referral to the mental health crisis team), or any information about future plans to collect these data, e.g. after implementation of KardiaMobile 6L.[53, 54] We did not identify any studies which reported information about the effects of using KardiaMobile 6L on the secondary clinical effectiveness outcome, time from decision to prescribe to treatment, and this outcome was not included in either of the two unpublished pilot project reports.[53, 54]

There was some evidence, from two unpublished pilot project reports,[53, 54] indicating benefits for KardiaMobile 6L in relation to secondary outcome measures, such as service user acceptability/preference, time taken to conduct an ECG and costs. This evidence may be considered as supportive of the need for further research to inform a full evaluation of the clinical and cost effectiveness of KardiaMobile 6L. However, it should be noted that the evidence provided in the two unpublished pilot project reports,[53, 54] was methodologically weak and subject to substantial uncertainty; further details are provided in Sections 4.2 and 5.2 of this report. The proportion of service users requiring antipsychotic medication, for whom ECG assessment of QT interval is clinically indicated, who accept an ECG and/or in whom and ECG is successfully completed, is also a potentially important secondary outcome measure. We consider assessment of this outcome measure to be important because, during scoping discussions with service users and clinical experts, and in survey results provided in the two unpublished pilot project reports,[53, 54] a preference for KardiaMobile 6L was indicated which was based on a perception that the device was less intrusive, easier to use and offered greater dignity and privacy than conventional 12-lead ECG. Given that

these preferences form an important part of the value proposition for KardiaMobile 6L, it is important to understand the extent to which preferences expressed may translate into increased acceptance and completion of ECG examinations in practice. Unfortunately, this outcome measure was not assessed by any of the published or unpublished studies identified and included in this report. Nationally, the baseline rate of ECG recording in service users who require antipsychotic medication is unclear; the limited national audit data available on the monitoring of side effects of patients prescribed antipsychotics in the UK, does not include ECG provision as one of the reported measures.[57] An recent article, submitted for publication and provided AiC by one of the SCMs for this topic (GC), reported a one-week service evaluation to investigate compliance with ECG monitoring on adult (>18 years) psychiatric inpatient wards in the Yorkshire and Humber Region.[58] The study aimed to assess the proportion of service users who received an ECG, the average delay between admission and ECG completion, and the common reasons for delay.[58] There were [redacted] service users from [redacted] wards caring for adults in [redacted] different Trusts, were included. Participating wards were working with [redacted]. The study found that [redacted] of service users admitted during the study period did not receive an ECG at any point during their stay, and of those who did receive an ECG, [redacted] experienced a delay of >24 hours.[58] These proportions were higher for service users on antipsychotic medication [redacted] and for service users on high dose antipsychotics [redacted][58] Where a specific reason was given for non-completion of an ECG, the most common reported reasons were [redacted] specifically, that the patient was [redacted] in [redacted] of instances.[58] Although falling outside the inclusion criteria for this EVA, because it did not report an evaluation of KardiaMobile 6L, this study provides a source of baseline data about ECG completion rates in a relevant population and important indication of the potential for improvement.[58]

The estimates of the costs associated with KardiaMobile 6L and 12-lead ECG and the costs savings reported for KardiaMobile 6L, provided in the two unpublished project reports from pilots undertaken in UK NHS Foundation Trusts,[53, 54] are subject to high levels of uncertainty (further details are provided in Sections 4.6 and 5.1 of this report). The possible relative annual Trust-wide costs of the two devices range from a cost increase of £1,074.79 (ERG calculation) to [redacted] associated with using KardiaMobile 6L.

Evidence to inform a full Diagnostic Assessment, including cost effectiveness modelling

We did not identify any studies that reported data for the outcome measures needed to inform a full Diagnostic Assessment, including cost effectiveness modelling. There were no data about the clinical diagnostic accuracy of KardiaMobile 6L for the detection of QTc prolongation in service users who

require antipsychotic medication. In particular, there were no data to inform estimates of the clinical sensitivity/rule-out reliability of the device; if KardiaMobile 6L were used to triage for and rule-out QT prolongation, we do not know how many people with QTc prolongation may be missed.

We did not identify any studies, randomised controlled trials (RCTs), controlled clinical trials (CCTs), or observational before and after (implementation) studies that assessed the effects of using KardiaMobile 6L versus 12-lead ECG on cardiac or psychiatric outcomes, or measures of HRQoL. Neither of the two unpublished project reports, which described UK NHS pilots of KardiaMobile 6L, reported any information about future plans to collect clinical outcomes data, e.g. after implementation of KardiaMobile 6L.[53, 54]

The available evidence about the UK costs of KardiaMobile 6L compared to 12-lead ECG, in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication, is highly uncertain.[53, 54]

Development of a cost effectiveness model was outside the scope of this EVA and, hence, no additional targeted searches were undertaken to inform model parameters. Additional information needed to inform cost effectiveness modelling could include: costs and utilities associated with relevant cardiac and psychiatric outcomes; effects of 12-lead ECG evaluation versus no ECG evaluation of QT interval, before prescribing antipsychotic medication, on cardiac and psychiatric outcomes; effects of 12-lead ECG evaluation versus no ECG, for monitoring QT interval in service users requiring ongoing antipsychotic medication, on cardiac and psychiatric outcomes; risk of adverse cardiac outcomes associated with QT prolongation in service users who are receiving antipsychotic medication; risk of adverse psychiatric outcomes in service users for whom antipsychotic medication is delayed, changed, or discontinued consequent upon the conduct or findings of an ECG assessment.

6. CONCLUSIONS

6.1 Implications for service provision

As anticipated during the scoping phase of this assessment and reflected in the decision to undertake an EVA, there is insufficient evidence to support a full Diagnostic Assessment evaluating the clinical and cost effectiveness of KardiaMobile 6L, in the context of QT interval-based cardiac risk assessment for service users who require antipsychotic medication.

The evidence to inform the aims this EVA (i.e. to assess whether the device has the potential to be clinically and cost effective) was also limited and it remains unclear whether KardiaMobile 6L has adequately demonstrated sufficient evidence of potential advantage(s) over current practice to justify further research to inform assessment of its clinical and cost effectiveness. **It is important to note that unpublished reports, used to inform the majority of the research questioned defined for this EVA, concern pilot projects which were not designed to be used in wider evaluations of KardiaMobile 6L for use in the NHS, such as the current EVA.**

6.2 Suggested research priorities

The following additional studies may be useful, to adequately inform/reduce the uncertainty in EVA for this topic:

- Technical validation studies in the relevant population and setting – studies should be undertaken to establish whether QT interval, measured using KardiaMobile 6L, can reliably reproduce the QT interval measured using 12-lead ECG. These studies should be undertaken in representative populations of service users who require antipsychotic medication (including those in whom it would usually be difficult to obtain an adequate ECG). The ECGs should be taken, using both methods, in the same patients, and the ECG examinations should be undertaken by healthcare professionals who are representative of those who would be expected to undertake the examination in real world clinical practice. In addition to measures of agreement for QT interval, such studies should record the technical failure rates, or proportion of ECGs judged to be inadequate for clinical decision making, for both methods.

- Comparison of time taken to complete an ECG examination using KardiaMobile 6L versus 12-lead ECG – an empirical comparison of the time taken to complete an ECG examination using KardiaMobile 6L versus 12-lead ECG should be undertaken. Time taken to complete ECG examinations should be measured in representative populations of service users who require antipsychotic medication (including those in whom it would usually be difficult to

obtain an adequate ECG) and where ECG examinations are undertaken by healthcare professionals who are representative of those who would be expected to undertake the examination in real world clinical practice. Measurements should include a) actual ECG recording time and b) staff travel time. A reliable comparison between KardiaMobile 6L versus 12-lead ECG could be achieved either by completing both examinations in all patients with the order of examination randomised (to control for possible effects of patient fatigue), or by randomising patients or locations to KardiaMobile 6L or 12-lead ECG. For designs where all participants do not receive ECG examination by both methods; studies should also record the success rate/rate of requirement for subsequent 12-lead ECG associated with KardiaMobile 6L.

- Assessment of the effects of using KardiaMobile 6L on the up-take/acceptance of ECG by service users – before and after observational (implementation) studies of KardiaMobile 6L should assess the proportion of service users requiring antipsychotic medication, for whom ECG assessment of QT interval is clinically indicated, who accept an ECG and/or in whom and ECG is successfully completed. It may be that these data could be obtained from records associated with the two UK NHS pilots of KardiaMobile 6L described in this report,[53, 54] although it is unclear whether any baseline data (pre-piloting of KardiaMobile 6L) are available for the relevant NHS Foundation Trusts.

- Assessment of the preferences of service users and healthcare professionals – a more reliable evaluation of preferences could be obtained from prospective survey studies, using survey instruments and methods designed with consideration to recognised sources of bias[59, 60] and established good practice for survey methods[61] and reporting.[62]

- Assessment of the UK costs associated with KardiaMobile 6L versus 12-lead ECG – estimates of the relative costs of KardiaMobile 6L versus 12-lead ECG, when used as specified in the decision problem, should be calculated based on measured (rather than estimated) time to complete each examination, for the relevant healthcare professionals and should include all relevant costs for each diagnostic pathway (e.g. follow-up 12-lead ECG in the proportion of patients for whom this requirement has been recorded in real world practice). It should be ascertained whether the per patient rate of follow-up 12-lead ECGs is obtainable from records associated with the two UK NHS pilots of KardiaMobile 6L described in this report.[53, 54]

The following studies could provide the additional data needed to inform a full Diagnostic Assessment, including cost effectiveness modelling:

- Diagnostic cohort studies evaluating the clinical accuracy of KardiaMobile 6L for the detection of QTc prolongation – these studies should evaluate the performance of KardiaMobile 6L, when used by healthcare professionals who are representative of those who would use the device in real world clinical practice. Studies should be conducted in representative populations of service users who require antipsychotic medication (including those in whom it would usually be difficult to obtain an adequate ECG). It is important to evaluate the clinical accuracy of the device in the population specified by the decision problem because diagnostic accuracy may be affected the by underlying prevalence of the target condition and by other population characteristics, such as ability to remain still during the examination. Similarly, measures of accuracy obtained when the device is used by healthcare professionals with levels of expertise and experience which are not representative of real world practice (e.g., interpretation by consensus of multiple cardiologists) may not be reproducible in the community of inpatient psychiatry settings relevant to the decision problem. Diagnostic cohort studies should also record the technical failure rates, or proportion of ECGs judged to be inadequate for clinical decision making, for both methods.

  Qualitative staff survey information[54] indicated that manual calculation of QTc and confidence about doing this was a key area of concern for staff, and affected the willingness of some staff to use the device; this issue was emphasised by CNTW project leads, as key for the potential implementation of the device (verbal communication from Jonathan Richardson, Stewart Little, and Nicola Orkney of CNTW to MW on 16/06/2022). AliveCor have indicated (see Section 2.2) that it is their intention to develop an algorithm to support automatic calculation of QTc; it may therefore be considered appropriate to await the release of this algorithm and to evaluate the clinical diagnostic accuracy of the device in the context of its use.

- Observational studies, evaluating the effects of implementing KardiaMobile 6L in relevant UK clinical settings, may also be of interest.

  Before conducting observational before and after (implementation) studies or pilot studies of a new technology, it is important to ensure that the potential risks of implementing the technology in the relevant NHS setting have been adequately assessed. This is problematic

for the example of KardiaMobile 6L for the assessment of QT interval in service users requiring antipsychotic medication because we have not been able to identify any data to estimate the clinical accuracy of the device for this target condition (in any population). The numbers of service users with QTc prolongation who might be missed, in a pilot or implementation study where KardiaMobile 6L was relied upon to rule out QTc prolongation is, therefore, unknown. A possible approach to considering the potential relative risks (in terms of service users with QTc prolongation which is not detected) of implementing KardiaMobile 6L versus doing nothing may be to estimate the proportion of service users with QTc prolongation who are not being picked up by current practice, because although recommended, 12-lead ECG is not always completed in practice. This number could be estimated from the product of the prevalence of QTc prolongation in the relevant population and the proportion of service users not currently receiving 12-lead ECG (unpublished study data described in Section 5.3). The proportion of service users with QTc prolongation who are not being picked up by current practice gives an indication of the minimum false negative rate that KardiaMobile 6L would need to achieve in order for it to be a potential improvement over current practice.

As is the case for diagnostic cohort studies, the way in which the technology is implemented is critical to the utility of observational, before and after implementation studies for UK decision making. The populations assessed and the way in which the intervention (KardiaMobile 6L) is used and interpreted during the study period should reflect the way in which it will be used in real world clinical practice; for example, healthcare professionals involved in the study should reflect the disciplines, training and experience of those expected to use KardiaMobile 6L in real world clinical practice. The study design should also reflect the way in which KardiaMobile 6L is intended to be used for clinical decision making; for example, if it is intended to be used as a triage test, patients in whom an abnormality is observed using KardiaMobile 6L should receive follow-up 12-lead ECG and those with a normal KardiaMobile 6L examination should receive no further investigations at that time, with all patients being followed-up to assess outcomes. Observational comparative studies provide a lower level of evidence with respect to the effects of an intervention than RCTs. Where observational study designs are used to provide estimates of effect, it is therefore important to control, as far as possible, for potential confounding factors (factors other than the ECG method that may affect the outcome or outcomes being assessed), for example, by matching participants in the intervention and comparator groups on key risk factors. It is also important that the care pathway remains unchanged, other than with respect to the

implementation of KardiaMobile 6L. Studies of the effects of the implementation of KardiaMobile 6L should measure clinical outcomes (e.g. adverse cardiac outcomes, duration of psychotic episode) alongside intermediate outcomes such as the proportion of service users who accept an ECG and/or in whom and ECG is successfully completed and time to appropriate intervention, and should report outcomes for test negative as well as test positive patients (i.e. outcomes should be reported for all study participants irrespective of whether or not QTc prolongation was identified and/or confirmed by follow-up 12-lead ECG and irrespective of the care received subsequent to testing).

- Cluster-RCTs, where inpatient and outpatient centres prescribing antipsychotics are randomised to implement KardiaMobile 6L or to continue with current practice, would offer a more methodologically robust approach to evaluating the effects of implementation as defined above. Stratification may be required in order to ensure that all relevant types of centre (e.g., inpatients and outpatient settings, general adult psychiatry, older adult psychiatry, forensic psychiatry) are represented in both study arms.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

Clinical Effectiveness Searches

Database	Date Span	Hits retrieved
Medline + Med in P	1946 -2022/04/25	3207
Embase	1974-2022/04/25	3816
PubMed-not-MEDLINE	1946-2022/05/17	180
PubMed	up to 2022/05/18	728
CDSR + CDSR P	up to 2022/04/Iss 4	40
CENTRAL	up to 2022/03/Iss 3	390
DARE	up to March 2015	2
HTA (CRD)	up to March 2018	4
CINAHL	1881-2022/04/27	886
PsycInfo	1806-2022/04/Wk 3	79
KSR Evidence	up to 2022/04/26	41
Epistemonikos	up to 2022/04/27	23
INAHTA	up to 2022/04/27	30
NIHR HTA	up to 2022/04/27	37
PROSPERO	up to 2022/04/26	33
INPLASY	up to 2022/04/27	1
LILACS	up to 2022/04/28	430
DOAJ	up to 2022/05/25	55
European Heart Journal – Digital health	Up to 2022/05/22	63
ClinicalTrials.gov	up to 2022/04/27	291
EUCTR	up to 2022/04/27	101
WHO ICTRP	up to 2022/04/28	121
ScanMedicine	up to 2022/04/28	259
Northern Light	2010 -2022/Wk 16	165
MedRxiv	up to 2022/04/27	145
Total		**11127**

MEDLINE (Ovid) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily: 1946-2022/04/25

Searched 26.4.22

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. (48356)

2 exp Electrocardiography / or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (272158)

3 1 and 2 (1151)

4 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (2291)

5 or/3-4 (3407)

6 exp animals/ not (exp animals/ and humans/) (4998919)

7 (letter or editorial or comment).pt. (2056043)

8 5 not (6 or 7) (3207)

Embase (Ovid): 1974-2022/04/25

Searched 26.4.22

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. (59823)

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. (402153)

3 1 and 2 (1877)

4 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (2379)

5 or/3-4 (4172)

6 animal/ (1571378)

7 animal experiment/ (2802350)

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. (7232812)

9 or/6-8 (7232812)

10 exp human/ (23537816)

11 human experiment/ (572513)

12 or/10-11 (23539828)

13 9 not (9 and 12) (5478029)

14 5 not 13 (4018)

15 (letter or editorial or note).pt. (2836000)

16 14 not 15 (3816)

MEDLINE(Ovid) PubMed-not-MEDLINE: 1946-2022/05/17

Searched 18.5.22

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. (9168)

2 exp Electrocardiography/ or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (10731)

3 1 and 2 (114)

4 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (78)

5 or/3-4 (186)

6 exp animals/ not (exp animals/ and humans/) (1)

7 (letter or editorial or comment).pt. (140866)

8 5 not (6 or 7) (180)

PubMed (NLM) (Internet): up to 2022/05/18
Searched 18.5.22

9 #7 and #8 728

8 (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 4,680,678

7 #5 or #6 9,251

6 (KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*) 2,706

5 #1 and #4 6,598

4 #2 or #3 274,648

3 Electrocardiography[MeSH Terms] 213,442

2 (Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*) 274,648

1 (portable or hand-held or handheld or "6 lead*" or "lead 6" or "leads 6" or "six lead" or "six channel*" or "6 channel*" or 6l or "6 l") 301,635

Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2022/04/Iss 4

Cochrane Database of Systematic Reviews (CDSR) Protocols (Wiley): up to 2022/04/Iss 4

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2022/03/Iss 3

Searched 26.4.22

#1 (portable or hand?held or handheld or 6?lead* or lead?6 or leads?6 or six?lead or six?channel* or 6?channel* or 6l or 6?l) 6727

#2 (Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*) 33251

#3 MeSH descriptor: [Electrocardiography] explode all trees 8998

#4 #2 or #3 33357

#5 #1 and #4 266

#6 (KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*) 176

#7 #5 or #6 431

CDSR retrieved 38 records

CDSR Protocols retrieved 2 records

CENTRAL retrieved 390 records

DARE (CRD)(https://www.crd.york.ac.uk/CRDWeb/): up to March 2015

HTA (CRD)(https://www.crd.york.ac.uk/CRDWeb/): up to March 2018

Searched 26.4.22

1 (portable or hand held or handheld or 6 lead* or lead 6 or leads 6 or six lead or six channel* or 6 channel* or 6l or "6 l") 197

2 MeSH DESCRIPTOR Electrocardiography, Ambulatory EXPLODE ALL TREES 34

3 (Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*) 669

4 #2 OR #3 669

5 #1 AND #4 8

6 ((KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*)) 1

7 #5 OR #6 9

8 (#7) IN DARE 2

9 (#7) IN NHSEED 3

10 (#7) IN HTA 4

DARE retrieved 2 records

HTA retrieved 4 records

CINAHL (EBSCO): 1881-2022/04/27

Searched 27.4.22

Advanced search, All fields

S7 S5 OR S6 886

S6 (KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*) 224

S5 S1 AND S4 674

S4 S2 OR S3 59,015

S3 (Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*) 59,015

S2 MH Electrocardiography 43,849

S1 (portable or hand?held or handheld or 6?lead* or lead?6 or leads?6 or six?lead or six?channel* or 6?channel* or 6l or 6?l) 29,304

APA PsycInfo (Ovid): 1806-2022/04/Wk3

Searched 26.4.22

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. (4210)

2 exp Electrocardiography/ or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (5251)

3 1 and 2 (47)

4 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (34)

5 or/3-4 (79)

KSR Evidence (https://ksrevidence.com/): up to 2022/04/26

Searched 26.4.22

1 (portable or hand held or handheld or 6 lead* or lead 6 or leads 6 or six lead or six channel* or 6 channel* or 6l or "6 l") in All text 3165 results

2 (Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*) in All text 684 results

3 #1 and #2 in All text 37 results

4 (KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*) in All text 6 results

5 #3 or #4 in All text 41 results

Epistemonikos (https://www.epistemonikos.org/): up to 2022/04/27

Searched 27.4.22

Advanced search Limits: Systematic Review / No Cochrane reviews

Keywords Title & Abstract	Hits
(title:((portable OR "hand held" OR handheld OR "6 lead" OR "6 leads" OR "lead 6" OR "leads 6" OR "six lead" OR "six leads" OR "six channel" OR "6 channels" OR "6 channel" OR 6l OR "6 l")) OR abstract:((portable OR "hand held" OR handheld OR "6 lead" OR "6 leads" OR "lead 6" OR "leads 6" OR "six lead" OR "six leads" OR "six channel" OR "6 channels" OR "6 channel" OR 6l OR "6 l"))) AND (title:((Electrocardiogram* OR electrocardiograph* OR ECG OR ECGs OR cardiogram* OR cardiograph* OR EKG OR EKGs OR electriccardiogram*)) OR abstract:((Electrocardiogram* OR electrocardiograph* OR ECG OR ECGs OR cardiogram* OR cardiograph* OR EKG OR EKGs OR electriccardiogram*)))	16
(title:((KardiaMobile* OR Kardia* OR KardiaBand OR KardiaPro OR AliveCor*)) OR abstract:((KardiaMobile* OR Kardia* OR KardiaBand OR KardiaPro OR AliveCor*)))	7
Total	**23**

INAHTA (https://www.inahta.org/hta-database/): up to 2022/04/27

Searched 27.4.22

Advanced search

All fields	Hits
("Electrocardiography"[mhe] or (Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*)) AND ((portable or hand?held or handheld or 6?lead* or lead?6 or leads?6 or six?lead or six?channel* or 6?channel* or 6l or 6?l))	29
KardiaMobile* OR Kardia* OR KardiaBand OR KardiaPro OR AliveCor*	1
Total	**30**

NIHR HTA (https://www.journalslibrary.nihr.ac.uk/): up to 2022/04/27

Searched 27.4.22

Search terms	Journal reports	Research Projects
ECG	6	24
ECGs	0/2	0/4
Electrocardiogram	1/3	3/11

electrocardiograph	0/4	3/5
Total	**7**	**30**

NIHR HTA retrieved 37 records

PROSPERO (CRD): up to 2022/04/26

Searched 26.4.22

#1 Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram* 1007
#2 MeSH DESCRIPTOR Electrocardiography EXPLODE ALL TREES 71
#3 #1 OR #2 1022
#4 portable or hand held or handheld or 6 lead* or lead 6 or leads 6 or six lead or six channel* or 6 channel* or 6l or "6 l" 574
#5 #3 AND #4 22
#6 (KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*) 12
#7 #5 OR #6 33

INPLASY (Internet) (https://inplasy.com/): up to 2022/04/27
Searched 27.4.22

Keyword	Hits
(Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs OR electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	1
(KardiaMobile OR KardiaBand OR KardiaPro OR AliveCor)	0
Total	**1**

Literature in the Health Sciences in Latin America and the Caribbean (LILACS) (Internet) (http://regional.bvsalud.org/php/index.php?lang=en): up to 2022/04/28
Searched: 28.4.22

Limited LILACs only

((Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*) AND (portable or "hand held" or handheld or "6 lead*" or "lead 6" or "leads 6" or "six lead" or "six channel*" or "6 channel*" or 6l or "6 l")) OR ((KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*))

LILACS retrieved 430 records

Directory of Open Access Journals (DOAJ) (https://doaj.org/): up to 2022/05/25
Searched 25.5.22

Keywords	In Title	In Abstract
Kardia	0	14
kardiaMobile	1	7

AliveCor	6	27
Total	**7**	**48**

DOAJ retrieved 55 hits

European Heart Journal – Digital health (https://academic.oup.com/ehjdh/): up to 2022/05/19
Searched 19.5.22

Keywords	Hits
Kardia*	20
6L	6
AliveCor*	11
ECG AND hand-held	4
ECG AND six	24
ECG AND 6 lead	61*(Please note: would not display past page 1 of results only able to access first 20 results)
Electrocardiogram AND six	26
Total	**152**
Total after dedupe & missing results	**63**

NIH ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov/): up to 2022/04/27
Searched 27.4.22

Expert search	Hits
(portable OR handheld OR hand held OR "6 lead" OR "6-lead" OR "6 leads" OR "lead 6" OR "leads 6" OR "six lead" OR "six leads" OR "six channel" OR "six channels" OR "6 channel" OR "6 channels" 6l OR "6 l") AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs OR electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	242
(KardiaMobile OR KardiaBand OR KardiaPro OR AliveCor)	49
Total	**291**

EU Clinical Trials Register (EUCTR) (Internet)
Searched 27.4.22

Expert search	Hits
(portable OR handheld OR hand held OR "6 lead" OR "6-lead" OR "6 leads" OR "lead 6" OR "leads 6" OR "six lead" OR "six leads" OR "six channel" OR "six channels" OR "6 channel" OR "6 channels" 6l OR "6 l") AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs OR electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	101
(KardiaMobile OR KardiaBand OR KardiaPro OR AliveCor)	0
Total	**101**

WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/search/en/): up to 2022/04/28
Searched 28.4.22

Advanced search option

Keywords	Hits
Title: (portable OR handheld OR hand held) AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs)	(3 record for) 3 trials found
Intervention: (portable OR handheld OR hand held) AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs)	(11 records for) 11 trials found
Title: (portable OR handheld OR hand held) AND (electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	(15 record for) 15 trials found
Intervention: (portable OR handheld OR hand held) AND (electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	(45 records for) 44 trials found
Title: (6 lead OR 6-lead OR 6 leads OR lead 6 OR leads 6 OR six lead OR six leads) AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs*)*	(1 record for) 1 trial found
Intervention: (6 lead OR 6-lead OR 6 leads OR lead 6 OR leads 6 OR six lead OR six leads) AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs*)*	(15 record for) 14 trials found
Title: (6 lead OR 6-lead OR 6 leads OR lead 6 OR leads 6 OR six lead OR six leads) AND (electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	(4 record for) 4 trials found
Intervention: (6 lead OR 6-lead OR 6 leads OR lead 6 OR leads 6 OR six lead OR six leads) AND (electrocardiography OR ECG OR ECGs OR cardiogram OR cardiograph OR EKG OR EKGs OR electriccardiogram)	(38 record for) 37 trials found
Title: (six channel OR six channels OR 6 channel OR 6 channels) AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs)	(0 record for) 0 trials found
Intervention: (six channel OR six channels OR 6 channel OR 6 channels) AND (Electrocardiogram OR Electrocardiograms OR electrocardiograph OR electrocardiographs)	(1 record for) 1 trial found
Title: KardiaMobile OR KardiaBand OR KardiaPro OR AliveCor	(4 records for) 4 trials found
Intervention: KardiaMobile OR KardiaBand OR KardiaPro OR AliveCor	(32 records for) 32 trials found
Total	**166**
Total after deduplication	**121**

ScanMedicine (Internet) (https://scanmedicine.com/): up to 2022/04/27
Searched: 27.4.22

Keywords	Hits
KardiaMobile* | Kardia* | KardiaBand | KardiaPro | AliveCor*	108
ECG + 6L	7
ECG + "6 lead"	13
ECG + "hand held"	24
ECG + portable	70
Electrocardiogram + portable	22
Electrocardiogram + "hand held"	12
Electrocardiogram + "6 lead"	2
Electrocardiogram + 6L	1
Total	**259**

Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2022/Wk16
Searched 26.4.22

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).af. (3801)
2 (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).af. (9338)
3 1 and 2 (60)
4 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).af. (109)
5 3 or 4 (165)

MedRxiv (Internet) (https://www.medrxiv.org): up to 2022/04/27
Searched 27.4.22

Advanced search

Abstract or title (match any word)	**Hits**
Electrocardiogram Electrocardiograms electrocardiograph electrocardiographs ECG ECGs cardiogram cardiograph EKG EKGs	144
KardiaMobile KardiaBand KardiaPro AliveCor	1/3
Total	**147**
Total without duplicates	**145**

Cost Effectiveness Searches

Database	**Date Span**	**Hits retrieved**
Medline + Med in P	1946 -2022/04/26	28
Embase	1974-2022/04/26	257
CEA Registry	up to 2022/04/28	44
RePEc	up to 2022/04/28	125
NHS EED	up to 2005/03	1
Total		**455**

Antipsychotics + ECGs + Costs (No A)

MEDLINE (Ovid) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily: 1946-2022/04/26
Searched 27.4.22

1 exp Electrocardiography/ or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (272187)
2 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (2293)
3 (CardioSecur or "Personal MedSystems GmbH").ti,ab,ot,hw. (3)
4 (D-Heart or "D Heart").ti,ab,ot,hw. (171)
5 ("RhythmPad GP" or CurAlive).ti,ab,ot,hw. (0)
6 or/1-5 (274143)
7 exp Antipsychotic Agents/ or (antipsycho$ or anti-psycho$ or neuroleptic$).ti,ab,ot. (149938)
8 ((major or butyrophenone) adj3 (tranquiliz$ or tranquilis$)).ti,ab,ot. (211)
9 (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. (2608)
10 (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,rn. (1414)
11 (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,rn. (26942)
12 (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,rn. (28145)
13 Methotrimeprazine/ or (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,rn. (1090)
14 (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,rn. (5629)
15 (aripiprazole or abilify or abilitat or opc 14597 or opc 31 or opc14597 or opc31 or "129722−12−9").ti,ab,ot,hw,rn. (4776)
16 (Asenapine or org 5222 or org5222 or saphris or secuado or sycrest or "65576−45−6" or "85650−56−2").ti,ab,ot,hw,rn. (483)

17 (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,rn. (13804)
18 (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,rn. (1575)
19 (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,rn. (535)
20 (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,rn. (1639)
21 (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,rn. (11522)
22 (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,rn. (1605)
23 (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,rn. (11085)
24 (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,rn. (6394)
25 (brexpiprazole or opc 34712 or opc34712 or rexulti or rxulti or "913611−97−9").ti,ab,ot,hw,rn. (271)
26 (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,rn. (313)
27 (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,rn. (571)
28 (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,rn. (375)
29 (Zuclopenthixol or cis clopenthixol or cisordinol or sedanxol or z clopenthixol or "53772−83−1").ti,ab,ot,hw,rn. (342)
30 or/7-29 (173851)
31 economics/ (27450)
32 exp "costs and cost analysis"/ (257457)
33 economics, dental/ (1920)
34 exp "economics, hospital"/ (25558)

35 economics, medical/ (9195)
36 economics, nursing/ (4013)
37 economics, pharmaceutical/ (3063)
38 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (938314)
39 (expenditure$ not energy).ti,ab. (34020)
40 (value adj1 money).ti,ab. (35)
41 budget$.ti,ab. (32959)
42 or/31-41 (1098733)
43 ((energy or oxygen) adj cost).ti,ab. (4515)
44 (metabolic adj cost).ti,ab. (1599)
45 ((energy or oxygen) adj expenditure).ti,ab. (27538)
46 or/43-45 (32619)
47 42 not 46 (1091218)
48 letter.pt. (1178093)
49 editorial.pt. (602942)
50 historical article.pt. (368305)
51 or/48-50 (2128461)
52 47 not 51 (1052283)
53 6 and 30 and 52 (28)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Embase (Ovid): 1974 to 2022/04/26
Searched 27.4.22

1 exp neuroleptic agent/ or exp atypical antipsychotic agent/ or (antipsycho$ or anti-psycho$ or neuroleptic$).ti,ab,ot. (288561)
2 ((major or butyrophenone) adj3 (tranquiliz$ 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. (8403)
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. (6303)
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. (51556)

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. (66728)
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. (5687)
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. (26546)
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. (18025)
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. (1802)
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. (36526)
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. (5896)
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. (2834)
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. (6771)
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. (40459)
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. (5475)
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. (40396)
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. (12967)
19 (brexpiprazole or opc 34712 or opc34712 or rexulti or rxulti or "913611−97−9").ti,ab,ot,hw,tn. (715)
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. (827)
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. (2094)
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. (1055)
23 (Zuclopenthixol or cis clopenthixol or cisordinol or sedanxol or z clopenthixol or "53772−83−1").ti,ab,ot,hw,tn. (2929)
24 or/1-23 (309037)
25 exp Electrocardiogram/ or exp electrocardiography/ or (Electrocardiogram$ or electrocardiograph$ or ECG or ECGs or cardiogram$ or cardiograph$ or EKG or EKGs or electriccardiogram$).ti,ab,ot,hw. (402165)
26 (KardiaMobile$ or Kardia$ or KardiaBand or KardiaPro or AliveCor$).ti,ab,ot,hw. (2379)
27 (CardioSecur or "Personal MedSystems GmbH").ti,ab,ot,hw. (9)
28 (D-Heart or "D Heart").ti,ab,ot,hw. (374)
29 ("RhythmPad GP" or CurAlive).ti,ab,ot,hw. (1)
30 or/25-29 (404178)
31 24 and 30 (6485)
32 health-economics/ (34200)
33 exp economic-evaluation/ (332620)
34 exp health-care-cost/ (317364)
35 exp pharmacoeconomics/ (217952)
36 or/32-35 (703617)
37 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1245105)
38 (expenditure$ not energy).ti,ab. (46018)
39 (value adj2 money).ti,ab. (2728)
40 budget$.ti,ab. (43331)
41 or/37-40 (1286035)
42 36 or 41 (1633007)
43 letter.pt. (1220949)
44 editorial.pt. (724072)
45 note.pt. (891248)
46 or/43-45 (2836269)
47 42 not 46 (1504929)
48 (metabolic adj cost).ti,ab. (1714)
49 ((energy or oxygen) adj cost).ti,ab. (4764)
50 ((energy or oxygen) adj expenditure).ti,ab. (34798)
51 or/48-50 (40110)
52 47 not 51 (1496696)
53 exp animal/ (28477822)
54 exp animal-experiment/ (2828547)
55 nonhuman/ (6869106)

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. (6134952)
57 or/53-56 (30586996)
58 exp human/ (23540271)
59 exp human-experiment/ (573121)
60 58 or 59 (23542341)
61 57 not (57 and 60) (7045737)
62 52 not 61 (1357340)
63 31 and 62 (257)

Economics terms based on Costs filter:
Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from: http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase

NHS Economic Evaluation Database (NHS EED) (CRD): up to March 2015
Searched 27.4.22

1 MeSH DESCRIPTOR Electrocardiography EXPLODE ALL TREES 303 Delete
2 ((Electrocardiogram* or electrocardiograph* or ECG or ECGs or cardiogram* or cardiograph* or EKG or EKGs or electriccardiogram*)) 669 Delete
3 ((KardiaMobile* or Kardia* or KardiaBand or KardiaPro or AliveCor*)) 1 Delete
4 ((CardioSecur or "Personal MedSystems GmbH")) 0 Delete
5 ((D-Heart or "D Heart")) 0 Delete
6 (("RhythmPad GP" or CurAlive)) 0 Delete
7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 675 Delete
8 (#7) IN NHSEED 285 Delete
9 MeSH DESCRIPTOR Antipsychotic Agents EXPLODE ALL TREES 720 Delete
10 ((antipsycho* or anti-psycho* or neuroleptic*)) IN NHSEED 188 Delete
11 ((major or butyrophenone) adj3 (tranquiliz* or tranquilis*)) IN NHSEED 0 Delete
12 ((pimozide or antalon or r 6238 or opiran or orap or pimocide or pimoride or pimozide or pizide or "2062?78?4")) IN NHSEED 0 Delete
13 ((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")) IN NHSEED 9 Delete
14 ((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")) IN NHSEED 40 Delete

15 ((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")) IN NHSEED 57 Delete
16 ((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")) IN NHSEED 2 Delete
17 MeSH DESCRIPTOR Methotrimeprazine EXPLODE ALL TREES 0 Delete
18 ((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")) IN NHSEED 40 Delete
19 ((aripiprazole or abilify or abilitat or opc 14597 or opc 31 or opc14597 or opc31 or "129722?12?9")) IN NHSEED 22 Delete
20 ((Asenapine or org 5222 or org5222 or saphris or secuado or sycrest or "65576?45?6" or "85650?56?2")) IN NHSEED 2 Delete
21 ((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")) IN NHSEED 51 Delete
22 ((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")) IN NHSEED 5 Delete
23 ((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")) IN NHSEED 2 Delete
24 ((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")) 14 Delete
25 ((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")) 269 Delete
26 ((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")) 33 Delete
27 ((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")) 318 Delete
28 ((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")) 42 Delete
29 ((brexpiprazole or opc 34712 or opc34712 or rexulti or rxulti or "913611?97?9"))0 Delete
30 ((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")) 12 Delete
31 ((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")) 0 Delete
32 ((Zuclopenthixol or cis clopenthixol or cisordinol or sedanxol or z clopenthixol or "53772?83?1")) 24 Delete
33 (#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32) 916 Delete
34 (#8 and #33) IN NHSEED 1 Delete

CEA Registry (http://www.cearegistry.org): up to 2022/04/28
Searched: 28.4.22

Keywords:
ECG OR ECGs OR Electrocardiogram OR electrocardiograph OR Electrocardiograms OR electrocardiographs OR electrocardiography

CEA retrieved 20 ratios
CEA retrieved 24 utilities

Research Papers in Economics (RePEc) (Internet) (http://repec.org/): up to 2022/04/28
Searched 28.4.22

Searched via IDEAS database (https://ideas.repec.org/)
Keywords in title:
(Electrocardiogram | electrocardiograph | ECG | ECGs | EKG | EKGs | electriccardiogram)

IDEAS retrieved 125 records

APPENDIX 2: QUADAS-2 ASSESSMENTS

Study: Azram 2021[14]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Prospective study of cardiology inpatients and outpatients. The only exclusion criteria were refusal or inability to provide informed consent

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	NA
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**

B. APPLICABILITY

The study was conducted in cardiology patients with a documented indication for ECG (no asymptomatic screening patients were included). The study did not include any patients where the indication for ECG was initiation of antipsychotic medication or monitoring during antipsychotic use.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

12-lead ECG was performed first, followed immediately by KardiaMobile 6L ECG. KardiaMobile ECG was performed, in triplicate, by a cardiologist and two cardiac physiologists. ECGs were anonymised and presented in random order for interpretation.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	NA
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD/COMPARATOR

A. RISK OF BIAS

12-lead ECG was performed first, followed immediately by KardiaMobile 6L ECG. 12-lead ECG was performed, in triplicate, by a cardiologist and two cardiac physiologists. ECGs were anonymised and presented in random order for interpretation.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Analysis was not possible for all leads, for either ECG method, data were reported by lead rather than by patient

Did all patients receive ECG both methods?	Yes
Was the time period between ECGs appropriate?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Kleijman 2021[30]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Prospective study of patients referred to a genetic hearty rhythm clinic; unclear whether patients were recruited consecutively. No inclusion or exclusion criteria reported.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	NA
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

The study was conducted in patients referred to a genetic hearty rhythm clinic. The study did not include any patients where the indication for ECG was initiation of antipsychotic medication or monitoring during antipsychotic use.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

KardiaMobile 6L ECG was performed, by patients, in controlled conditions, and interpreted by cardiologists who were blinded to subject identifiers and details of the study. KardiaMobile 6L and 12-lead ECGs were evaluated in separate cohorts, using different subject identifiers, and in a randomised order.

Were the index test results interpreted without knowledge results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	NA
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD/COMPARATOR

A. RISK OF BIAS

12-lead ECGs were interpreted by cardiologists who were blinded to subject identifiers and details of the study. KardiaMobile 6L and 12-lead ECGs were evaluated in separate cohorts, using different subject identifiers, and in a randomised order.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Eleven (1.6%) patients were excluded from the analysis because >30 minutes had elapsed between KardiaMobile 6L and 12-lead ECG recordings.

Did all patients receive ECG both methods?	Yes
Was the time period between ECGs appropriate?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Krzowski 2021[51]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Prospective study of consecutive patients on a tertiary care cardiology ward. No inclusion or exclusion criteria reported.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	NA
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

The study was conducted in tertiary care cardiology inpatients. The study did not include any patients where the indication for ECG was initiation of antipsychotic medication or monitoring during antipsychotic use.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

KardiaMobile 6L ECG was performed by experienced technicians. All ECG recordings were assessed, blinded, by experienced clinicians.

Were the index test results interpreted without knowledge results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	NA
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD/COMPARATOR

A. RISK OF BIAS

12-lead ECGs were performed by experienced technicians. All ECG recordings were assessed, blinded, by experienced clinicians.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

One patient (1%) did not receive KardiaMobile 6L ECG, due to Parkinson's disease-related tremor. KardiaMobile 6L and 12 lead ECG recordings were made consecutively

Did all patients receive ECG both methods?	No
Was the time period between ECGs appropriate?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Minguito-Carazo 2021[36]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Healthy control patients from a study of COVID-19 patients. No selection criteria were reported

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	NA
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

The comparative data from this study were derived from healthy control patients. The study did not include any patients where the indication for ECG was initiation of antipsychotic medication or monitoring during antipsychotic use.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

No details of who recorded the KardiaMobile 6L ECG were reported. All ECG recordings were reviewed by at least one cardiologist. It was not clear whether cardiologists interpreting KardiaMobile 6L ECG recordings had access to 12-lead ECG recordings.

Were the index test results interpreted without knowledge results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	NA
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD/COMPARATOR

A. RISK OF BIAS

No information was reported regarding the conduct of 12-lead ECGs. All ECG recordings were reviewed by at least one cardiologist. It was not clear whether cardiologists interpreting 12-lead ECG recordings had access to KardiaMobile 6L ECG recordings.

Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

All healthy control patients received ECG by both methods.

Did all patients receive ECG both methods?	Yes
Was the time period between ECGs appropriate?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Orchard 2021[40]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Healthy, asymptomatic athletes, with no existing cardiac diagnoses or family history of conditions associated with sudden cardiac death. No inclusion or exclusion criteria were reported.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	NA
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Study of healthy athletes. The study did not include any patients where the indication for ECG was initiation of antipsychotic medication or monitoring during antipsychotic use.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

No details of who recorded the KardiaMobile 6L ECG were reported. All ECG recordings were reviewed by four expert cardiologists. It was not clear whether cardiologists interpreting KardiaMobile 6L ECG recordings had access to 12-lead ECG recordings.

Were the index test results interpreted without knowledge results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	NA
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD/COMPARATOR

A. RISK OF BIAS

No information was reported regarding the conduct of 12-lead ECGs. All ECG recordings were reviewed by four expert cardiologists. It was not clear whether cardiologists interpreting 12-lead ECG recordings had access to KardiaMobile 6L ECG recordings.

Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

All participants received ECG by both methods within one hour.

Did all patients receive ECG both methods?	Yes
Was the time period between ECGs appropriate?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

APPENDIX 3: DETAILS OF EXCLUDED STUDIES WITH RATIONALE

To be included in the review studies had to fulfil the following criteria:

Research Question 1:	***'What is the accuracy/technical performance of KardiaMobile 6L, where the target condition is QTc prolongation, determined by standard 12-lead ECG (the reference standard method)?***
Population:	Any
Setting:	Any
Index Test:	KardiaMobile 6L
Comparator:	None
Reference Standard:	12-lead ECG
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, concordance (of QT interval determined by KardiaMobile 6L with that determined by 12-lead ECG), test failure rates and reasons for failure
Study design:	Diagnostic cohort studies or observational, non-inferiority/equivalence studies for concordance

Research Question 2:	***'What are the clinical effects of using KardiaMobile 6L, compared with 12-lead ECG or no ECG, on clinical outcomes (cardiac and psychiatric)?'***
Population:	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
Index Test:	KardiaMobile 6L
Comparator:	12-lead ECG or no ECG
Reference Standard:	Not applicable
Outcomes:	Cardiac outcomes (arrhythmias, sudden cardiac death), psychiatric outcomes, hospitalisations (cardiac of psychiatric), referrals to mental health crisis teams, other adverse effects of antipsychotic medication, HRQoL, change to treatment decision, time from decision to prescribe to treatment
Study design:	RCTs, CCTs or observational before and after (implementation) studies

Research Question 3:	***'What are the effects of using KardiaMobile 6L on service user acceptability/satisfaction and on training and workflow issues?'***
Population:	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 OR Healthcare professionals or others delivering ECG assessment of QT-based cardiac risk, in settings applicable to the above population (training and workflow)
Setting:	Any
Index Test:	KardiaMobile 6L
Comparator:	12-lead ECG or no comparator
Reference Standard:	Not applicable
Outcomes:	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
Study design:	RCTs, CCTs and comparative or non-comparative observational studies

Research Question 4:	***'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?'***
Population:	Any UK population
Setting:	Any
Index Test:	KardiaMobile 6L
Comparator:	12-lead ECG or no comparator
Reference Standard:	Not applicable
Outcomes:	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
Study design:	RCTs, CCTs and comparative or non-comparative observational studies

Research Question 5:	***'What existing, published cost effectiveness studies are available about QT interval assessment for service users who require antipsychotic medication?'***
Population:	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
Index Test:	Any ECG device
Comparator:	Any other ECG device or no comparator
Reference Standard:	Not applicable
Outcomes:	Quality-adjusted life years
Study design:	Studies reporting a full economic analysis

Table 9 summarises studies which were screened for inclusion based on full text publication, but which failed to fulfil all inclusion criteria, for any research question.

Table 9: Studies excluded based on full text screening

Study Details	Research Question	Study Design	Population	Index Test	Comparator	Reference Standard	Outcome
Abellas Sequeiros, 2021[23]	1	N	Y	Y	NA	N	N
	2	Y	N	Y	NA	NA	N
	3	Y	N	Y	NA	NA	N
	4	Y	N	Y	NA	NA	N
	5	N	N	Y	NA	NA	N
Collins, 2021[24]	1	N	Review article abstract only, no data or references				
	2	N					
	3	N					
	4	N					
	5	N					
Giudicessi, 2021[26]	1	N	Transcript of a podcast, no data				
	2	N					
	3	N					
	4	N					
	5	N					
Hoehns, 2020[27]	1	N	Y	N	NA	N	N
	2	Y	N	N	NA	NA	Y
	3	Y	N	N	NA	NA	Y
	4	Y	N	N	NA	NA	N
	5	N	N	N	NA	NA	N
Hoehns, 2021[28]	1	N	Y	N	NA	N	N
	2	Y	N	N	NA	NA	Y
	3	Y	N	N	NA	NA	Y
	4	Y	N	N	NA	NA	N
	5	N	N	N	NA	NA	N
Karacan, 2019[29]	1	Y	Y	N	NA	Y	Y

Study Details	Research Question	Study Design	Population	Index Test	Comparator	Reference Standard	Outcome
	2	Y	N	N	Y	NA	N
	3	Y	N	N	Y	NA	N
	4	Y	N	N	Y	NA	N
	5	N	N	N	NA	NA	N
Ko, 2021[31]	1	N	Y	N	NA	N	N
	2	Y	N	N	NA	NA	Y
	3	Y	N	N	NA	NA	N
	4	Y	N	N	NA	NA	N
	5	N	N	N	NA	NA	N
Koltowski, 2021[32]	1	Y	Y	N	NA	Y	Y
	2	Y	N	N	Y	NA	N
	3	Y	N	N	Y	NA	N
	4	Y	N	N	Y	NA	N
	5	N	N	N	NA	NA	N
Liu, 2022[34]	1	N	Y	Y	NA	N	N
	2	Y	N	Y	N	NA	N
	3	Y	N	Y	N	NA	N
	4	Y	N	Y	N	NA	N
	5	N	N	Y	N	NA	N
Mercer, 2020[35]	1	Y	Y	N	NA	Y	Y
	2	Y	N	N	Y	NA	N
	3	Y	N	N	Y	NA	N
	4	Y	Y	N	Y	NA	N
	5	N	N	N	NA	NA	N
Noseworthy, 2021[37]	1	Y	Y	Y	NA	Y	Y
	2	Y	N	Y	Y	NA	N
	3	Y	N	Y	Y	NA	N

Study Details	Research Question	Study Design	Population	Index Test	Comparator	Reference Standard	Outcome
	4	Y	N	Y	Y	NA	N
	5	N	N	Y	NA	NA	N
Rotella, 2016[44]	1	N	Y	N	NA	Y	N
	2	N	N	N	Y	NA	N
	3	N	N	N	Y	NA	N
	4	N	N	N	Y	NA	N
	5	N	N	N	NA	NA	N
Singh, 2020[45]	1	N	Review article				
	2	N					
	3	N					
	4	N					
	5	N					
Stavrakis, 2017[46]	1	Y	Y	Y	NA	Y	N
	2	Y	N	Y	Y	NA	N
	3	Y	N	Y	Y	NA	N
	4	Y	N	Y	Y	NA	N
	5	N	N	Y	NA	NA	N
Stavrakis, 2017 [47]	1	Y	Y	Y	NA	Y	N
	2	Y	N	Y	Y	NA	N
	3	Y	N	Y	Y	NA	N
	4	Y	N	Y	Y	NA	N
	5	N	N	Y	NA	NA	N
Stavrakis, 2022[48]	1	Y	Y	N	NA	Y	Y
	2	Y	N	N	N	NA	N
	3	Y	N	N	N	NA	N
	4	Y	N	N	N	NA	N
	5	N	N	N	NA	NA	N

Study Details	Research Question	Study Design	Population	Index Test	Comparator	Reference Standard	Outcome
Titus-Lay, 2019 [49]	1	Y	Y	N	NA	Y	Y
	2	Y	N	N	Y	NA	N
	3	Y	N	N	Y	NA	N
	4	Y	N	N	Y	NA	N
	5	N	N	N	NA	NA	N
Titus-Lay, 2019[50]	1	Y	Y	N	NA	Y	Y
	2	Y	N	N	Y	NA	N
	3	Y	N	N	Y	NA	N
	4	Y	N	N	Y	NA	N
	5	N	N	N	NA	NA	N
N = no; NA = not applicable; Y = yes							

APPENDIX 4: POTENTIALLY RELEVANT ONGOING STUDIES

1. Medical University of Lodz 2022 (NCT05206825) Evaluation of Electrocardiography Performed With Mobile ECG Devices in Cardiac Patients and Healthy Volunteers[63] – status, *'not yet recruiting'*

2. University of Oklahoma 2021 (NCT05053243) Clinical Validation of the AliveCor Kardia 12L and 6L Devices[64] – status, *'active not recruiting'*

3. Leeds Teaching Hospitals NHS Trust and Leeds & York Partnership NHS Foundation Trust 2021 (NCT04227418) An Evaluation of the Safety and Clinical Utility of Handheld ECG Technology in Psychiatry[65] – status, up-date provided by an SCM (MT), *'recruitment affected by COVID, unlikely to be completed'*

4. Leeds Teaching Hospitals NHS Trust 2020 (NCT04468477) EVALECGcardio Study[66] – status, up-date provided by an SCM (MT), *'This has been published and has been included in one of your references. The paper is Azram et al'*[14]

5. Leeds Teaching Hospitals NHS Trust 2022 (NCT05324111) VaLidation of the Simple Adaptation of the Kardia 6L ECG Recorder to Obtain Chest leAd equivaLents: a Multi-centre International (LOCAL-ECG) Study; on Behalf of the Africa Heart Rhythm Association Investigators[67] – status, up-date provided by an SCM (MT), *'Recruitment has just started and will take some time so unlikely to report on time for this'*

APPENDIX 5: COPIES OF STAFF SURVEYS USED IN THE CNTW PILOT STUDY

AliveCor KardiaMobile 6L Staff Feedback 2021

Required

1.Please enter your name

2.Please select the date of completion of this survey using the calendar icon

2022

3.Did you use the AliveCor KardiaMobile 6L device?

- Yes
- No

4.How many times did you record an ECG using the KardiaMobile 6L device?

5.Did the use of the AliveCor KardiaMobile 6L device change the clinical outcome for your patient?

- Yes
- No

6.Please explain how the AliveCor KardiaMobile 6L device changed the clinical outcome for your patient.

7.Thinking about using AliveCor KardiaMobile 6L device in the future, how likely are you to use AliveCor KardiaMobile 6L device as part of service users' treatment if it were available?

- Extremely likely
- Somewhat likely
- Neither likely nor unlikely
- Somewhat unlikely
- Extremely unlikely

8.How likely are you to recommend using AliveCor KardiaMobile 6L device as part of a service users' treatment to other members of your team?

- Extremely likely
- Somewhat likely
- Neither likely nor unlikely
- Somewhat unlikely
- Extremely unlikely

9.Has COVID-19 impacted the usage of the AliveCor KardiaMobile 6L device?

- Yes
- No

Submit

KardiaApp - Staff Questionnaire

Questionnaire for staff to complete whilst conducting ECGs with remote KardiaMoblie 6L device

Required

1.Please enter your name:

2.Which team are you in?

Select your answer

3.What band are you?

- Band 2
- Band 3
- Band 4
- Band 5
- Band 6

4.Did the patient refuse to take an ECG using the AliveCor KardiaMobile 6L device?

- Yes
- No

5.Approximately, and on average, how long would you spend with each patient when carrying out a usual ECG? (please select one)

- Less than 5 minutes
- 5-10 minutes
- 11-20 minutes
- 21-31 minutes
- 32+ minutes

6.Approximately, and on average, how long would you spend with each patient when carrying out a usual ECG, including travel time? (please select one)

- Less than 40 minutes
- 40-50 minutes
- 51+ minutes
- N/A

7.Approximately, and on average, how long have you spent with each patient when carrying out a ECG with the AliveCor KardiaMobile 6L (app & device)? (please select one)

- Less than 5 minutes
- 5-10 minutes
- 11-20 minutes
- 21-31 minutes
- 32+ minutes

8.Approximately, and on average, how long would you spend with each patient when carrying out using the AliveCor KardiaMobile 6L device, including travel time? (please select one)

- Less than 40 minutes
- 40-50 minutes
- 51+ minutes
- N/A

9.Approximately how much clinical time has been saved using the KardiaMobile 6L device? (Please enter time in minutes below)

10.What clinical indication accounts for the majority of ECGs you perform? (please select one)

- I am not always aware of the indication
- Before starting dementia medications
- Monitoring dementia medications
- Before starting antipsychotics
- Monitoring antipsychotics

11.Please select your preferred option in relation to each of the following:

	Regular ECG	KardiaMobile 6L
Easiest		
Dignity and privacy		
Most intrusive		
Most comfortable		

	○	
	○	
Ease of sending information to the relevant professional		
	○	
	○	
Overall preference		
	○	
	○	

12.Did you encounter any difficulties when using the ECG KardiaMobile 6L device?

- ○ Yes
- ○ No

13.In future tests, would you prefer a regular ECG or ECG KardiaMobile 6L for QT monitoring?

- ○ Regular ECG
- ○ ECG KardiaMobile 6L

14.Please state any suggestions you may have for further improvement.

15.Please state any benefits that you have identified by using the KardiaMobile 6L?

16.Were you able to get any feedback from the patient during their ECG KardiaMobile 6L appointment?

- ○ Yes
- ○ No

17.Has the patient had the regular ECG before?

- ○ Yes
- ○ No

18.If yes, please select their preferred option in relation to each of the following:

	Regular ECG	KardiaMobile 6L
Easiest		
	○	
	○	
Dignity and privacy		
	○	
	○	
Most intrusive		
	○	

Most comfortable	
Ease of sending information to the relevant professional	
Overall preference	

19.In future tests, would the patient prefer a regular ECG or ECG KardiaMobile 6L for QT monitoring?

- Regular ECG
- ECG KardiaMobile 6L

Submit

APPENDIX 6: PRISMA CHECK LIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Preceding table of contents
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Sections 3.2 and 3.5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 3.1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 3.3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 3.3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Sections 3.2 and 3.3
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding	Section 3.3

Section and Topic	Item #	Checklist item	Location where item is reported
		sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 3.4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Section 3.3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section 3.5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 3.5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 3.5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1 and section 4.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 3

Section and Topic	Item #	Checklist item	Location where item is reported
Study characteristics	17	Cite each included study and present its characteristics.	Section 4.1 and Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 4.2 and Appendix 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Sections 4.3 to 4.7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 4.2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Sections 4.2 to 4.7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 5.1
	23b	Discuss any limitations of the evidence included in the review.	Sections 5.2 and 5.3
	23c	Discuss any limitations of the review processes used.	Section 5.2.1
	23d	Discuss implications of the results for practice, policy, and future research.	Section 6
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO registration:

Section and Topic	Item #	Checklist item	Location where item is reported
			CRD42022336695
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	PROSPERO
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA (no amendments)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funded by NIHR
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	None

EAC costs and resource report

Work package number	RX312
Work package name	Kardiamobile 6L ECG costs and resource report
NICE Project Lead contact details	Frances Nixon [redacted]

Project definition

The purpose of this project is to produce a report on the costs and resource use associated with the use of the KardiaMobile 6L ECG device to measure QT interval in people having antipsychotic medication. NICE will use the report as part of the evaluation of the technology. The report may be sent to the diagnostics advisory committee as part of a package of evidence on the KardiaMobile 6L ECG device.

Document history

Version no.	Date	Author	Purpose
1.0	10 June 2022	Khanh Ha Bui Stephen McSwiney Anita Patel	First draft
2.0	17 June 2022	Julius Ohrnberger Stephen McSwiney Khanh Ha Bui Anita Patel	Second draft
3.0	28 June 2022	Julius Ohrnberger Stephen McSwiney Khanh Ha Bui Anita Patel	Third draft

Produced by: King's Technology Evaluation Centre (KiTEC), King's College London (KCL), Ipsos

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Dr. Rudolf Cardinal is a Consultant liaison psychiatrist at Cambridge and Peterborough NHS Foundation Trust

1. Background

The use of the KardiaMobile 6L ECG device to measure QT interval in people having antipsychotic medication was considered suitable for evaluation by the NICE Diagnostics Assessment Programme (DAP).

Antipsychotic medications are prescribed for a range of symptoms/conditions, with a variety of different treatment approaches, as summarised below.

- People who suffer from schizophrenia and associated disorders are recommended antipsychotic medication and cognitive behavioural therapy according to the CG178 clinical guideline (NICE, 2014a). Medication doses should start at lower range and are not recommended for people at increased risk of developing psychosis, or for preventing psychosis.
- People with bipolar disorder are offered antipsychotic medications such as haloperidol, olanzapine, quetiapine or risperidone during periods of mania according to the CG185 clinical guideline (NICE, 2014b). People with moderate or severe bipolar depression may be offered olanzapine or quetiapine. Antipsychotics may also be recommended for long-term use to prevent relapse.
- People with dementia who suffer from severe agitation, aggression or psychotic symptoms, or experience symptoms that cause severe distress may be offered antipsychotics. NICE also recommends conducting a structured assessment to explore possible reasons for the distress before considering antipsychotic medication (NICE, 2018). Recommendations include 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. Clinical experts advised that antipsychotics are usually a last resort if non-pharmacological interventions or de-escalation techniques are unsuccessful.
- People with depression who do not respond well to initial treatment with antidepressants are recommended antipsychotic medications such as aripiprazole, olanzapine, quetiapine or risperidone. The NICE guideline (NICE, 2009) cautioned that decisions to use antipsychotics in this manner should be made with care given that some antidepressants can also prolong the QT interval.

In current practice, patients who are treated with antipsychotic medications may need to be tested for risks of cardiac abnormalities before and during treatment. Signs of cardiac abnormalities can inform the choice of therapy and dosing, and can potentially avoid severe cardiac events. In primary and secondary care settings, 12-lead electrocardiogram (ECG) devices are used for screening and diagnostic purposes. ECG outcomes such as measurement of QT interval may be interpreted by the operator (for example, a GP), an algorithm provided by the manufacturer, or can be forwarded to a specialist nurse, consultant, or an external ECG interpretation service. ECGs have been shown to be effective in the detection of atrial fibrillation, diagnosis of patients with palpitations, and evaluation of QT interval. Usage of 12-lead ECG requires the individual to partially undress and use a conductive gel to create contact with the electrodes. However, [like others,] people taking antipsychotic medications may find it difficult to attend appointments at healthcare centres or may not be able to travel for ECG appointments.

The KardiaMobile 6L is a portable handheld 6-lead ECG device 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, which can then be sent via email to physicians. The device can be used in peoples' homes by community healthcare practitioners on home visits and does not require patients to travel. The technology might also benefit people taking antipsychotics who may experience stress or discomfort undressing for the traditional 12-lead ECG test. This could potentially improve attendance for ECG appointments, number of cardiac cases being detected, and reduce resource demand for 12-lead ECGs in hospitals or GP surgeries. In a published prospective study (Azram *et al.*, 2021), the Kardia 6L was demonstrated to perform closely to the gold standard 12-lead ECG in specific parameters (QT interval in all six leads, rhythm detection, PR interval, QRS duration, and cardiac axis). However, in cases where the outcome of the 6-lead ECG is unclear, or if other heart conditions such as ischaemia or left ventricular hypertrophy are suspected, a 12-lead ECG may be required as it provides more information for which 6-lead devices are still limited (Azram et al. 2021, Kleiman et al. 2021).

2. Diagnostic and care pathway

The National Clinical Audit of Psychosis (Royal College of Psychiatrists, 2017) recommended that people with psychotic disorders are assessed for risk of cardiovascular disease annually with an ECG test. The Royal College of Psychiatrists consensus stated that ECG is recommended for before and during patient's antipsychotic therapy when:

- high-risk antipsychotic medication is being considered (for example, pimozide, haloperidol or sertindole)

- high-dose or short-acting, parenteral antipsychotic drug therapy is to be used in an elderly patient or a patient with a history of cardiovascular disease. ECGs should be performed every few days following initiation of high-dose treatment or during a period of dose escalation, until it is judged that steady state concentrations have been reached. ECG and electrolyte assessment is recommended every few months at times of acute illness, when potentially interacting drugs are introduced or if the person experiences symptoms that could be due to arrhythmia (for example, fainting or seizure).

Additionally, both the NICE clinical guidelines on psychosis and schizophrenia in adults (NICE, 2014a) and the clinical guideline on bipolar disorder (NICE, 2014b) 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 or
- the service user is being admitted as an inpatient.

In the guidelines for the Management of QTc Prolongation in Adults Prescribed Antipsychotics (NHS Northern England Clinical Network, 2018), the flow diagram indicates that a baseline ECG should be done for all patients commencing antipsychotic medication. However, clinical experts suggested that ECGs are most

commonly done for inpatients or people with cardiac comorbidities or risk factors, but not for all people starting antipsychotics. Additionally, according to the Clinical Guidelines on the Management of Patients Developing QT Prolongation on Antipsychotic Medication (Lambiase *et al.*, 2019), actions to be taken according to QTc are as follows:

- QTc <440 ms (Men) or <470 ms (Women)

No action required– consider cardiac review if in doubt.

- QTc >440 ms (Men) or >470 ms (Women), but <500 ms

Consider reducing dose or switching to drug of lower effect; repeat ECG and consider cardiology review.

- QTc >500 ms

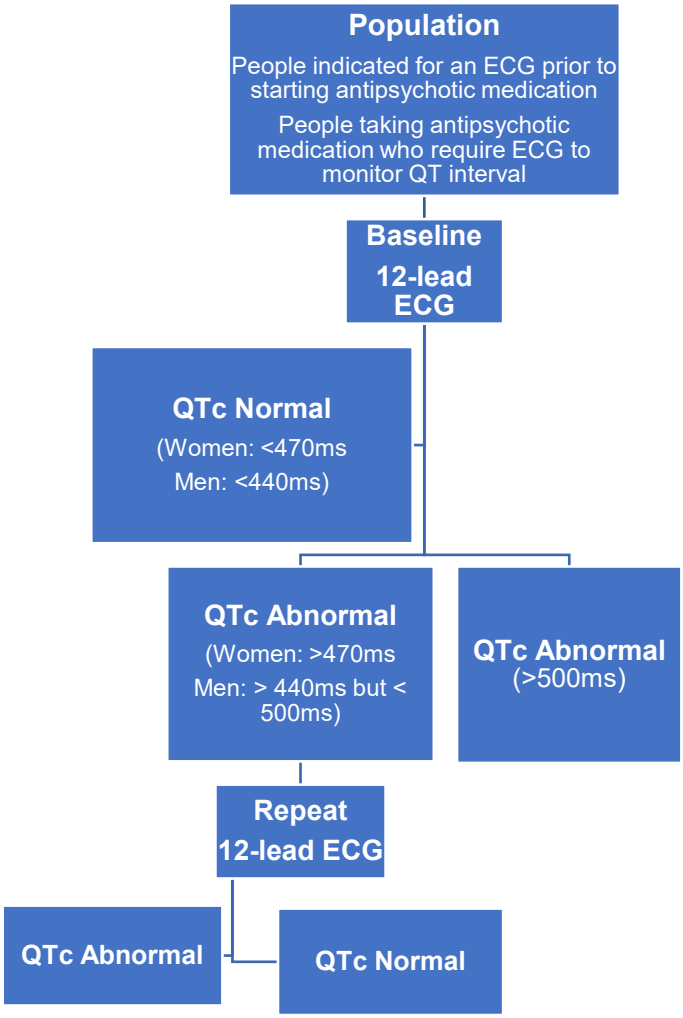
Stop suspected causative drug(s) and switch to drug with a lower effect: immediate cardiology review is needed. If the patient has syncope or pre-syncope, immediate ECG monitoring for ventricular arrhythmias should be performed.

- Abnormal T-wave Morphology

Review treatment. Consider reducing dose or switching the patient to a lower risk antipsychotic, i.e. lurasidone, cariprazine or brexpiprazole.

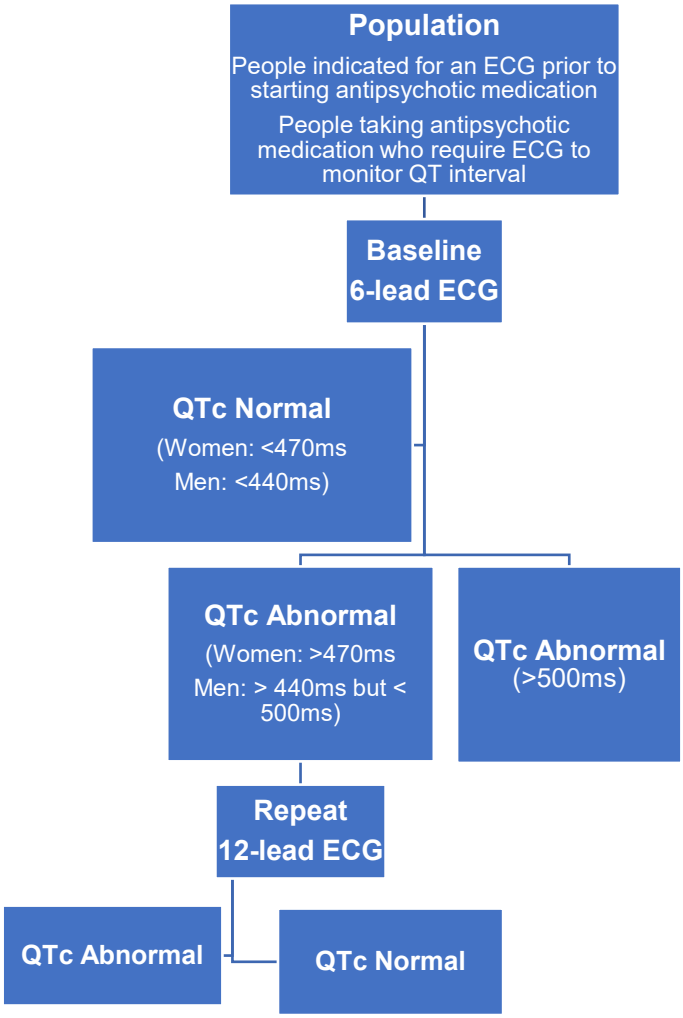
Adapting the guidelines from the NHS Northern England Clinical Networks, Figure 1 summarises the flow diagram for current practice on management of QTc prolongation in adults taking antipsychotic medication.

Figure 1. Flow diagram for management of QTc in adults prescribed antipsychotics in current practice with 12-lead ECG



In the intervention pathway where a KardiaMobile 6-lead ECG is adopted to obtain a baseline reading, clinical experts have stated that the traditional 12-lead ECG might be employed in cases where a repeat ECG is necessary. Figure 2 illustrates how the pathway could differ with the implementation of a 6-lead ECG according to experts' recommendations.

Figure 2. Flow diagram for management of QTc in adults prescribed antipsychotics using 6-lead ECG



After using the KardiaMobile device to obtain a baseline reading, , similarly to current practice, there may be instances where a repeat ECG will need to be taken, using the traditional 12L ECG. However, there were mixed views from clinical experts regarding which technology should be used for the repeat ECG, with some stating that a 6-lead ECG can be used for both stages provided that the result quality is good, hence a 12-lead ECG is not required.

As part of the KardiaMobile Pilot Study (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021) and [redacted]

[redacted] One clinical reason cited for using the 12L ECG after the KardiaMobile device was that the 12L ECG provides more in-depth information to aid staff making a clinical decision. Non-clinical reasons focused around not being able to obtain a reliable reading with the KardiaMobile device. Staff found that despite the longer time required to take a 12L ECG (30 seconds for a KardiaMobile device versus 60 seconds for a 12L ECG), when patients were agitated and restless the 12L ECG outperformed the KardiaMobile device as it was able to obtain clearer readings.

Potential reasons for a 12L ECG after using the 6L device:

- KardiaMobile Pilot Study
    - Poor reading/ not enough information
    - More in-depth information required when carrying out ECGs - the consultant psychiatrist within team prefered the paper ECG reports with full readings, not just the QTc for any atrial fibrillation
    - Patients would not maintain contact with both hands and knees for full 30 seconds, following placement of ECG electrodes patient allowed to rest on bed once relaxed ECG recorded. 12-lead took longer to record but provided clearer reading
    - Results needed clinician review, following which a 12L was performed
    - Used KardiaMobile as one-off for initiation of anti-psychotics but all patients were offered 12L ECG afterwards for regular monitoring
    - Unreliable reading, QTc not calculated
    - High QTc calculation
    - Erroneous pattern caused by patient movement made QTc interpretation difficult. 12L used to gauge accuracy of KardiaMobile device, two readings were different

[redacted]

Additionally, from the KardiaMobile Pilot Study, staff were also asked what types of service users they would not offer the KardiaMobile device to. Responses can be grouped into three broad groups of service users. The first group is those requiring a more detailed and/or full ECG report, which the KardiaMobile device cannot provide. This includes patients who suffer from addictions, eating disorders or have known cardiac problems. The second group of service users include those who are not able to hold still enough. This includes patients with marked tremors in their hands and patients who are agitated or restless. In these circumstances the KardiaMobile device is not able to obtain a good quality trace, making calculation and interpretation of the QT interval difficult. The final group of service users who staff would not offer the KardiaMobile device to would be anyone who is willing to accept the traditional 12L ECG. Staff stated that they would rather offer the 12L ECG and obtain a full report and, in their opinion, a more reliable reading; especially when there is no reason not to use a traditional 12L ECG. Traditional ECG is superior and they are not willing to compromise patients when not necessary.

3. Resource identification, measurement, and valuation

The cost and resource use information presented in Table 1 and Table 2 was initially informed by company information submission including device costs, academic studies, and the KardiaMobile pilot study. A rapid scoping review was further undertaken using MEDLINE, Google Scholar, and Google search engine for grey literature. Following the rapid review, remaining gaps in cost and resource use information were addressed through communications with clinical experts.

Table 1. Resource use for traditional 12-lead ECG and 6-lead ECG

Parameter	Value		Range		Source		Note
	12-lead ECG	6-lead ECG	12-lead ECG	6-lead ECG	12-lead ECG	6-lead ECG	
Average time spent to take ECG	24 minutes and 28 seconds	8 minutes and 28 seconds	Staff reported taking: < 5 minutes to > 32 minutes	Staff reported taking: < 5 minutes to > 32 minutes	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	To calculate average, midpoint of 47 minutes was used for the >32 minutes category
	Control group: 3 minutes and 38 seconds Covid group: 8 minutes and 39 seconds	Control group: 1 minutes and 33 seconds Covid group: 1 minutes and 47 seconds	Control group: SD of 34.4 seconds Covid group: SD of 94.1 seconds	Control group: SD of 29.7seconds Covid group: SD of 37.8 seconds	(Minguito-Carazo *et al.*, 2021)	(Minguito-Carazo *et al.*, 2021)	These estimates are significantly lower compared to those of the Pilot Study
	5 minutes	N/A	-	N/A	(Cancer Research UK, 2022)	N/A	Source study was unclear
	9 minutes	N/A	-	N/A	(Foster *et al.*, 1994)	N/A	The population was a patient group who received thrombolytic therapy
	30 minutes	< 1 minute	-	-	Clinical expert opinion	Clinical expert opinion	Expert opinion of clinical expert used for this report.
Staff band for taking ECG	Band 3, 6	Band 3, 6	-	-	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	Unclear whether staff bands 4 and 5 are relevant for taking ECG

Time to do QTc calculation (internal calculation)	3.5 minutes	3.5 minutes	-	-	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	Clinical expert stated that the 12-lead ECG does the QTc calculation. Although in some instances cardiologists like to manually calculate the QTc to double check
Number of requests for ECG interpretation to cardiology	20% (65%) of GP practices (non-recording) recording ECGs used secondary care for interpretation	N/A	-	N/A	(Wolff *et al.*, 2012)	N/A	General population and not specifically for anti-psychotic drug users; unit is GP practices; secondary care used as proxy for general interpretation need
Number of technical problems with ECG Machine	-	4%	-	-		(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	This only accounts for technical issues with the machine; there were further technical issues reported with the app, which are discussed below.
Proportion of traditional 12-lead ECGs required after KardiaMobile 6L	53%		47% to 60%		(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)		Pilot study saw 9 out of 15 required subsequent 12L ECGs. Validation Exercise saw 7 out of 16 require subsequent ECGs. Total of 16 out of 30 required subsequent ECGs Note: small sample size
Staff training time	Approx. 2 - 3 hours training module	2 training sessions (no indication of duration)	-	-	Clinical expert opinion	(Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	For 12-lead ECG: training module was delivered by band 6 nurses and above. For 6-lead ECG: First training session was

							delivered by consultant and senior clinical director. Second training session was delivered by consultant and chief clinical information officer

3.1 Time to take an ECG test

The KardiaMobile Pilot Study (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021) provides information on the average time spent per service user to take an ECG reading. This question was separately asked for the standard of care 12-lead ECG and the 6-lead KardiaMobile device. Those surveyed were able to choose time categories of: Less than 5 minutes, 5-10 minutes, 11-20 minutes, 21-31 minutes, and 32+ minutes. The average for each option was used alongside a mid-point of 47 minutes for the '32+ minutes' category to calculate the average time among the respondents. This method was used to compute averages for both the 12-lead ECG and the 6-lead KardiaMobile. The Pilot Study was not explicit in what the time input represents. It was implied that this is the time from when the patient enters the ECG room to when they leave the ECG room. Given this ambiguity, alternative sources were explored for information on the average time to perform a 12-lead and 6-lead ECG.

Estimates in the literature place the average time to undertake a 12-lead ECG between 5 and 10 minutes (Cancer Research UK, 2022; Foster et al., 1994; Minguito-Carazo et al., 2021). This is significantly lower compared to the average of about 24 minutes reported in the Pilot Study. One clinical expert suggested that due to the logistics of taking the ECG, a 12-lead ECG can take an average of up to 30 minutes.

Literature on the mean time to use the KardiaMobile device is more limited. Minguito-Carazo et al., 2021 observe an average time of an ECG with the KardiaMobile device at between 1 and 2 minutes, which is significantly lower than the reported average of 8.5 minutes in the Pilot Study. One clinical expert stated that a 6-lead KardiaMobile ECG can take under 1 minute, due to the KardiaMobile being non-invasive and having no contact points.

3.2 Staff band for taking ECG test

The NHS Agenda for Change pay band for staff that used the KardiaMobile device was collected from the Pilot Study, which suggested that band 3 staff are the main

users of the KardiaMobile device, and band 3 and band 6 staff are the common users of the 12-lead ECG.

3.3 Time to do QTc calculation

The average time of 3.5 minutes for a medical doctor to calculate the QTc was sourced from the KardiaMobile Pilot Study (2021) and is self-reported by the medical doctors. The calculation is the same for the 12-lead ECG and the 6-lead KardiaMobile device.

3.4 Number of requests for ECG interpretation to cardiology

A targeted search for the incidence of external ECG interpretation in the NHS was conducted. A qualitative study (Wolff ***et al.***, 2012) found that 20% of GP practices that record ECGs and 65% of GP practices which are not recording ECGs use secondary care for their interpretation. However, this study observed the general population instead of specific users of anti-psychotic medications. Another limitation of the study is that the authors included only GP practices from the North-East of England, limiting the external validity of findings to other regions. Furthermore, estimates from the study may be outdated as the study was conducted in 2012.

3.5 Staff training

Traditional 12-lead ECG training is typically taught as part of nursing or medical training, and as such the Trust would incur no specific cost for such training. According to expert opinion, it is common for staff who are band 6 and above to hold 12-lead ECG training sessions for band 3 and 4 staff, which would likely take 2-3 hours. However, given that this is a localised approach, 12-lead ECG training in one NHS Trust is not likely representative of other NHS Trusts.

The Pilot Study reports that 90 staff members undertook training sessions for the 6-lead ECG device. Two training sessions were held, although it is unclear whether all 90 staff members attended both days, and how long each training session lasted for. The first training session was led by a consultant and a senior clinical director. The second training session was held by a consultant and the chief clinical information

officer. The focus of the training in the KardiaMobile Pilot Study (2021) was ‘Underpinning Theory to Practice’ and a ‘Device Demonstration’.

3.6 Number of technical problems with 6-lead ECG

The Pilot Study identifies that 4% of staff members (2 out of 51) reported technical issues with the KardiaMobile device. These technical issues included sending the ECG from the KardiaMobile App and the trace being insufficient for interpreting the QTc. Across the whole Pilot Study, 42 support tickets were logged, 15 of which were clinical queriesand, of the 27 technical queries raised, only two were about the device; the remaining 25 were about either the KardiaMobile app or Outlook.

3.7 Proportion of traditional 12-lead ECGs required after KardiaMobile 6L

The proportion of traditional 12-lead ECGs required after the KardiaMobile ECG was informed by two studies. Firstly, the KardiaMobile Pilot Study (2021) reports that 60% (9 out of 15) of KardiaMobile ECGs required subsequent use of a 12-lead ECG. [redacted]

Overall, this suggests that 53% of the time (16 out of 30) a subsequent 12L ECG was required. However, it should be noted that the total sample size is 30, and is therefore not representative, and that there may have been variations across the studies in the drivers for undertaking a follow up 12-lead ECG. Reasons for using the standard 12L ECG following an ECG with the KardiaMobile 6L device are listed in section 2 page 10.

From clinical expert opinion, it was suggested that out of 200 6-lead ECGs, around 5% needed a subsequent 12-lead ECG. Only in cases where a 6-lead could not obtain a reading, or a result was borderline, a follow-up 12-lead ECG would be used. Furthermore, for the purpose of obtaining the QTc interval, the 12-lead ECG was suggested to only marginally outperform a 6-lead ECG.

Table 2. Cost parameters for traditional 12-lead ECG and 6-lead ECG

Parameter	Value		Range		Source		Note
	12-lead ECG	6-lead ECG	12-lead ECG	6-lead ECG	12-lead ECG	6-lead ECG	
Staff cost (per hour) for band 3	Community nurse: £25.90 Hospital nurse: £26.98	£25.90	-	-	(Curtis and Burns, 2017)	(Jones and Burns, 2021)	Band 3 nurse unit cost available in 2017 report; inflation adjusted to 2021 values using CPI inflator
Staff cost (per hour) for band 6	Community nurse: £55 Hospital nurse: £51	£55	-	-	(Curtis and Burns, 2017)	(Jones and Burns, 2021)	For 12-lead ECG: 2021 unit cost for band 6 nurse
Cost per internal QTc calculation (3.5 minutes)	£1.31	CT1 – CT2 - £1.18 CT3 and Band 8a - £1.50 Band 7 - £1.26	£1.31	CT1 – CT2 - £1.18 CT3 and Band 8a - £1.50 Band 7 - £1.26	(British Medical Association, 2022) (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	(British Medical Association, 2022) (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)	Assumes doctors work 37.5 hours per week. Then derive hourly wage to work out what 3.5 minutes of time costs. £1.31 is average of three values – could be improved using weighted average
Cost per QTc interpretation – Broomwell Healthwatch Service	£17.33		£14 - £21		(KardiaMobile Pilot Study, 2021)		Average of the pricing list for Broomwell Healthwatch service: £21- immediate interpretation, £17 - overnight interpretation, £14 - weekend interpretation
Opportunity cost for delivering the	3 hours of ECG training delivered by one band 6	-	-	-	(Jones and Burns, 2021)	-	Figure does not account for the cost of those attending

training (i.e. unit cost per hour for training instructor)	hospital (community) nurse would cost £153 (£165)						the training, ECG wear and tear and consumables .
Cost per ECG device	Unit cost of 12L ECG device: £2,231 in 2021 prices (estimated £2,000 in 2015 prices)	Kardia Mobile Device: £124.20 (exl. VAT) iPad Cost: £618.33 (exl. VAT) E1 and security Licence: £61.56 (exl. VAT)	-		(NICE, 2016)	AliveCor, Inc. (Company information request)	Total KardiaMobile cost of £964.87 including VAT. The Kardia app is free of charge. The KardiaMobile6L device requires a CR2016 coin cell battery which is recommended to be changed annually. The provided costs do not include maintenance cost, nor the cost to replace damaged or lost KardiaMobile devices/ iPads or 12L ECG parts.

3.8 Staff cost for taking ECG test

Band 3 and band 6 community and hospital nurses' hourly rates were sourced from the Unit Costs of Health & Social Care annual compendium compiled by the Personal Social Services Research Unit (PSSRU). Costs reported in the PSSRU compendium account for wider working activities and costs (e.g. overheads and paid leave) in addition to salary/hours worked. The Unit Costs of Health and Social Care (2017) provides information on the average cost per hour for band 3 staff. We used unit costs in 2017 values as those are the latest available PSSRU estimated unit costs for band 3 nurses. This has then been inflated to 2021 prices to ensure costs are in the same base year. The hourly staff cost for a band 6 was sourced from the Unit Costs of Health and Social Care (2021).

3.9 Cost of QTc interval calculation

The KardiaMobile Pilot Study (2021) estimates the cost for a medical doctor to calculate the QTc interval. The British Medical Association (2022) pay scales for doctors is used to derive an hourly wage[1]; which then can be used to work out the cost to calculate the QTc interval. The Pilot Study presents the cost per QTc calculation for four grades/ pay band: CT1-CT2 costs £1.18 per calculation, CT3 costs £1.50 per calculation and band 7 costs £1.26 per calculation. These values are then averaged to provide an estimate of £1.31 per QTc calculation.

3.10 Cost per QTc interpretation

The KardiaMobile Pilot Study (2021) identified that some teams within the Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust outsourced the QTc interval interpretation to the private provider Broomwell HealthWatch[2]. Costs ranged from £14 for a weekend interpretation to £21 for an immediate interpretation, with a mean cost of cost of £17.33.

[1] Annual salary broken down to find hourly rate based on 37.5-hour week. Note annual leave allowances and overheads are not accounted for in this calculation.

[2] Broomwell HealthWatch are an external company that provide an ECG calculation and interpretation service

3.11 Training costs

Using the PSSRU Unit Costs of Health and Social Care 2021 for the hourly cost of a band 6 nurse, the opportunity cost of time to deliver 3 hours of 12-lead ECG training amount to £165 for a band 6 community nurse (£153 for a band 6 hospital nurse). Further opportunity costs of time for the attendees of the training occur but are not considered in this figure. We note that these estimates are based on the information from the expert witness relating to the average time spent to train the use of 12-lead ECGs. It is plausible that different Trusts have different ways of delivering 12-lead ECG training; as such training costs are likely to vary by NHS Trust. It was not feasible to estimate the cost of 6-lead KardiaMobile ECG training due to the lack of information on the amount of time spent for training.

3.12 ECG device costs

The estimated costs for a standard 12-lead ECG amount to £2,231 in 2021 prices (estimated at £2,000 in 2015 prices) (NICE, 2016). AliveCor Inc. reported that the cost of the 6-lead KardiaMobile device is £124.20 excluding VAT, and £149.00 including VAT (company information request). The KardiaMobile Pilot Study (2021) further reports that each iPad costs £742 and the E1[3] and security licence for each iPad cost £73.87 and required renewal on an annual basis. The total cost per KardiaMobile device (including licences and iPad) are £964.87, accordingly. It should be noted that this does not account for ongoing licence costs (£73.87 per year), maintenance costs or replacement of lost/ broken devices. Furthermore, the KardiaMobile Pilot Study (2021) suggested that if Trust smartphones were used instead of iPads, then the iPads and licences would not be required.

3.13 Additional resource cost and use calculations

Table A1 in the appendix provides a list of the cost and use of prescribed antipsychotic medications and their use in the NHS in the financial year 2020/21.

[3] An E1 licence allows the iPad to access web-versions of Microsoft Office Applications (including Outlook) and allows access to cloud services such as OneDrive and Teams.

We have used simple calculations to provide further contextual information on the total number of ECG usage, the proportion of ECG usages prior to anti-psychotic drug treatment, the proportion of abnormal ECGs and associated follow-up costs among the population of anti-psychotic drug users in England. We present and discuss these findings alongside sourced information on the prevalence of anti-psychotic drug usage in section A3 of the appendix.

3.14 Parameters with uncertainty

There were instances where the provided information from NICE and our scoping search were unable to identify values for given parameters. These parameters include the time from ECG results to the initiation of antipsychotic medication and the cost of a missed ECG appointment. Neither the provided documents and literature from NICE nor our rapid scoping search identified information for the short-term cost of a missed ECG appointment from a health provider's perspective. However, one way to estimate the cost per missed appointment could be to use the opportunity cost of NHS staff time spent on an average ECG including the additional administrative cost for the replacement ECG. Further missing but relevant parameters are the completion rates of ECG appointments for ECG 12-lead and the 6-lead KardiaMobile device, and training costs for specifically the KardiaMobile device.

There are further instances where more work is required to reliably estimate parameters. This includes technical failure rates of 6-lead compared to 12-lead ECGs, training costs, the number of people who require an ECG before starting antipsychotic medication, the total number of ECGs recorded among the population of anti-psychotic drug users, and the number of people who require anti-psychotic medication.

4. Conclusion

This report aims to collect and synthesise evidence on the diagnostic and care pathway, and the costs and resource use of the KardiaMobile 6-lead ECG. The 6-lead ECG has been introduced to measure the QT interval in people prescribed with antipsychotic medication. Clinical experts suggested that ECG has the potential to

provide clinical benefits in target populations where antipsychotic medications may be prescribed long enough to reach steady state, for instance: schizophrenia and associated disorders, bipolar disorders, dementia, and depression. KardiaMobile is a portable handheld ECG device that offers comfort to people who might experience stress undressing for the traditional 12-lead ECG, potentially improves attendance for ECG appointment, reduces requirement for travelling, and reduces resource demand for 12-lead ECG.

4.1 Diagnostic and care pathway

In this report, the population in the pathway for ECG assessment in current practice includes all adults prescribed antipsychotics, following the final scope in NICE DAP (NICE, 2022) and as recommended in the NHS Northern England Clinical Network guideline. However, recommendations for application of ECGs vary across guidelines (e.g. the National Clinical Audit of Psychosis, the Royal College of Psychiatrists consensus, NICE clinical guidelines for psychosis and schizophrenia and for bipolar disorder) and practice. Clinical experts noted that there is currently no consensus, and assessment decision may vary depending on specific types of drugs and risk factors of individual or patient groups. According to experts' opinions, ECGs are most commonly done in cases where high-risk medications are prescribed, patients are in an older age group, or patients have history of cardiac comorbidities. While this report attempts to summarise the placement of ECG within a clinical pathway, further work may be required to map current practice, confirm best practice pathways and determine whether any sub-group analyses are relevant for further evaluation of KardiaMobile 6-lead ECG as a replacement of the 12-lead ECG.

Actions based on ECG/QTc may differ, both in terms of clinical follow-throughs from ECG results, and responses to an unclear ECG reading. The KardiaMobile device is introduced as a potential replacement for the traditional 12-lead ECG in measuring QT interval for people prescribed antipsychotics. However, there were mixed opinions from clinical experts. Some suggested that 6-lead ECG could be used to measure for baseline and repeat ECGs in cases when results show prolonged (abnormal) QT interval. Anecdotal evidence from a clinical expert recorded under 5% of patients' ECG requiring a 12-lead for confirmation following a 6-lead ECG in one hospital trust

annually. Other experts suggested the usage of 6-lead ECG as a screening tool, if detection shows abnormal QT interval, the traditional 12-lead ECG would be used for confirmation. According to the Azram et al. study, 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, a 12-lead ECG may be required. Available evidence indicated some hesitations about the reliability and depth of the 6-lead ECG reading and clinical experts stated that the traditional 12-lead ECG might be employed in cases where a repeat ECG is necessary (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021)

Potential issues with the usage of KardiaMobile device are highlighted from the Pilot Study and Validation Exercise. Surveyed staff suggested three types of service users who would not benefit from using the 6-lead ECG, including those requiring more detailed ECG report, those with movement disorders, and those who prefer the traditional 12-lead ECG (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, 2021). Despite staff's concerns about the reliability of the 6-L ECG from a study, patient preferences could differ since a 6-lead ECG does not require undressing. One clinical expert indicated that, in their service, the attendance rate is higher for 6L-ECG and that patients are sometimes more inclined to have an ECG with 6L. Differential rates of acceptability of the approaches would likely impact on take-up of ECGs and thus clinical decision making, care, costs and outcomes. Furthermore, [redacted] Nevertheless, further literature searches were unable to find parameter estimates for technical issues relevant to the use of KardiaMobile apart from qualitative data.

4.2 Resource identification, measurement, and valuation

The evidence review from this report suggested high levels of uncertainty for parameter values. Most parameters are observed or reported as single figures, lacking information of their distribution (i.e. information about their range such as 95%-confidence intervals or standard deviations/errors). This limits the interpretation and usability of the parameters for further studies. Additionally, there is a high degree of

between-parameter variation of identified potentially cost-driving key parameters such as the reported time for taking an ECG, the staff band taking ECGs, the requirements for external services to interpret ECG results, and the ECG-training time and cost.

The quality of identified parameter values is fundamentally impeded by the lack of existing quality studies and the availability of a broader range of information sources. Most of the populated parameters are either informed from the KardiaMobile Pilot Study (2021) or the clinical expert. The KardiaMobile pilot lacks both internal and external statistical validity, well specified questions to identify parameters values, and an appropriate statistical analysis to estimate parameter values and their uncertainty (e.g. standard errors or confidence intervals). The study further used a small sample size with a high degree of non-engaged pilot projects, and thus increased the risk of outliers driving study results. Other referenced studies either focus on general or different population groups or may present out-dated population estimates (e.g. Foster et al. (1994), Wolff et al. (2012), Minguito-Carazo et al. (2021)).

Whilst several resource use and cost parameters for ECG assessment were identified, there are insufficient quality studies on specific parameters relevant for conducting a cost effectiveness analysis of KardiaMobile e.g. the time between ECG results and the initiation of medication, the NHS costs for missed ECG appointments, completion rates of ECG appointments for ECG 12-lead and the 6-lead KardiaMobile device, and training costs. Based on the evidence provided on the resource use and cost parameters, further research and clinical trials are necessary to fill the evidence gaps and identify robust parameter estimates for cost effectiveness analysis.

5. References

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Appendix

A1: Discussion of Bazett and Friderica formula

The difference between the two corrections is that the Bazett formula uses reciprocal of the square root of the RR interval. The Fridericia formula uses the reciprocal of the cube root of the RR interval. It is argued that using the Bazett formula over-corrects at high rates, and under-corrects at low rates; meaning the Fridericia formula may be better at detecting atrial fibrillation and adverse outcomes (Goldman, 2020).

A2: Cost and use of antipsychotic medications in NHS communal care

Table A1 lists the cost and usage volume of prescribed antipsychotic medications in the NHS in the financial year 2020/21. Information were sourced from the NHS Prescription Cost Analysis (NHS Business Services Authority, 2021). The Prescription Cost Analysis provides details of the number of items and the Net Ingredient Cost of all prescriptions dispensed in the community in England. Medications prescribed in primary care make up most prescription costs in the NHS (60%) and will be most relevant for the study population of antipsychotic drug users requiring ECG monitoring as the majority won't be hospitalised. It should be noted that costs for medications prescribed in hospitals will differ. Furthermore, resource use and costs data for the drugs Asenapine, Loxapine, Prochlorperazine, and Brexpiprazole which were identified in the final scope in the NICE DAP were not identified in the Prescription Cost Analysis. The drugs Melperone, Ziprasidone, Benperidol, Fluphenazine, Pericyazine, Perphenazine, Promazine, and Thioridazine were not included in the scoping document but identified in the Prescription Cost Analysis.

Table A1. Antipsychotic drug cost and use in the NHS in the financial year 2020/2021

Type of antipsychotic drug	Total units (e.g. tables, capsules, vials, ampules) in the financial year 2020/2021	Cost per unit (£) in 2020/2021 values
Zuclopenthixol acetate	94	20.40
Risperidone	1,784,409	3.86
Olanzapine	2,578,090	3.60
Amisulpride	408,602	9.10
Quetiapine	4,062,455	7.87
Aripiprazole	1,395,011	4.96
Paliperidone	2,920	99.19
Melperone hydrochloride	1	1,083.00
Ziprasidone hydrochloride	4	293.40
Lurasidone	28,306	85.69
Cariprazine	1,402	78.02
Benperidol	4,184	73.79
Clozapine	3,880	45.17
Chlorpromazine hydrochloride	238,804	31.75
Flupentixol hydrochloride	34,572	5.92
Fluphenazine hydrochloride	82	284.16
Haloperidol	345,469	36.76
Levomepromazine maleate	35,433	32.43
Levomepromazine hydrochloride	133,392	15.65
Pericyazine	59,485	24.53
Perphenazine	333	123.42
Pimozide	3,542	14.72
Promazine hydrochloride	121,604	50.82
Zuclopenthixol hydrochloride	87,739	8.59
Sulpiride	104,580	24.01
Thioridazine	95	289.57
Trifluoperazine	33,717	54.50

A3: Additional ECG resource use and cost calculations

Prevalence of antipsychotic drug users in the English population

We did not identify data on the number of antipsychotic drug users in the English population. A study by Marston et al. (2014) estimates a population of 47,742

antipsychotic drug users in the UK primary care setting. Notably, less than 7,000 out of 13,941 prescribed first-generation agents had a diagnosis of psychosis or bipolar disorder (see table A2). The study uses cohort data from 2007 to 2011 and prevalence estimates are likely outdated. Further research on the prevalence of antipsychotic drug users in England is required to provide a reliable estimate.

ECG usage among the antipsychotic drug user population

The median number of ECGs performed prior to anti-psychotic drug initiation is in the range of 5-10 (midpoint value 7.5) per month and the median number of ECGs performed among antipsychotic drug users is in the range of 11-15 (midpoint value 13) per month among projects that took part in the KardiaMobile Pilot Study (see table A2). Using this information one can infer that about 58 percent of ECGs performed are intended for the pre-assessment of anti-psychotic drug usage.[4]

Extrapolating these figures to England based on a simple calculation, about 1,643 ECGs are recorded per month for pre-medical anti-psychotic drug assessment, with a total of 2,847 ECGs per month for the antipsychotic drug user population (see table A2).[5]

We note that this calculation has a strong degree of uncertainty and hence potential for bias, due to the stated limitations of the pilot study and the lack of clarity in the reporting of this information. We suggest collecting specific information to reliably estimate the two parameters.

Proportion of people with abnormal ECG results

Inferring from the KardiaMobile pilot study, 2.5 was the median of the number of times a second opinion from a cardiologist was required for a 12-lead ECG per three-month period.[6] No information could be found for the 6-lead ECG. Using figures of a median of 13 ECGs per project per month (see section 3.8), we can estimate that 2.5 times of out of 39 per three month period (or 6 percent of the ECGs) required consulting a cardiologist (see table A2). This can be a proxy measure for abnormal ECG results.

[4] Due to the skewedness of data we have used median values and not the average.

[5] To compute the total number of ECGs in England, we have multiplied the results by 219 which is the current number of healthcare trusts in England.

[6] We use a median due to the skewness of data.

We highlight again the high degree of uncertainty of this simple calculation, the data limitations, and the requirements to gather further and better data to reliably estimate such a parameter.

Table A2. Background information and calculations of the resource use of 12-lead ECGs

Parameters	Value	Range	Source
Total ECG usage for anti-psychotic drug users in England	2,847 ECGs per month	KardiaMobile Pilot Study 2021 and calculations	KardiaMobile Pilot Study 2021: median average of ECGs for anti-psychotic drug users per project is 13 per month (mid-point of range 11-15); The total number is derived taking the mid-point of 13 multiplied by 219 which is the number of healthcare trusts in England Strong uncertainty around this parameter estimate.
ECG usage prior to anti-psychotic drug treatment for anti-psychotic drug users in England	1,643 ECGs per month or 58 percent of performed ECGs for anti-psychotic drug users	KardiaMobile Pilot Study 2021 and calculations	KardiaMobile Pilot Study 2021: median average of ECGs for anti-psychotic drug users pre drug initiation is 7.5 (mid-point of range 5-10) per month per project. Total number derived taking 7.5 multiplied by 219 which is the number of healthcare trusts in England Strong uncertainty around this parameter estimate.
Proportion of abnormal ECG results among ECGs of anti-psychotic drug users	6 percent of ECGs; 171 ECGs per month in England (using figure computed for total ECG usage)	KardiaMobile Pilot Study 2021 and calculations	KardiaMobile Pilot Study 2021: reported median of 2.5 times projects required the second opinion of a cardiologist over a three-month period; assumed ECGs per 3 months: 39 informed from ECG usage data and median of 13 ECGs per month. 171 is derived by multiplying the total assumed numbers of ECGs (2,847) by 0.06. Our simple calculation has a high degree of uncertainty.,

Costs associated with cardiology follow-up appointments

Applying a 2019/2020 NHS reference cost of £142 per cardiologist consultation to our previously computed information of 6 percent out of the 2,847 (171 ECGs) ECGs recorded monthly in England requiring the assessment of a cardiologist, costs for the NHS in England amount to £24,282 per month (see table A3).

Table A3. Background information and calculations of the cost parameters for traditional 12-lead ECG

Average unit cost of a cardiologist consultation	£145.68 in 2021 prices (£142 for the financial year 2019/2020)	NHS reference cost (2019/2020)	
Total cost of NHS follow-up assessment by a cardiologist, per month	£24,911.28 in 2021 prices	Simple calculations	Using our calculation of 171 cases per month (see resource use table) multiplied by the unit cost for a cardiology consultation. High degree of uncertainty for this simple calculation.

Evidence overview: KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

This overview summarises the main issues the diagnostics advisory committee needs to consider. It should be read together with the final scope, the early value assessment report by Kleijnen Systematic Reviews and the cost and resource report by King's Technology Evaluation Centre (KiTEC).

1 Aims and scope

People taking antipsychotic medication may need testing for cardiac abnormalities before starting treatment and at regular intervals during treatment. Detecting cardiac abnormalities such as prolonged QT interval can inform choice of therapy, dosing, whether to stop therapy, and potentially avoid severe cardiac events.

Current practice to measure QT interval is to use 12-lead ECG devices in primary or secondary care centres. These need the person to partially undress, and use conductive gel on the skin to create contact with the electrodes. This can cause reluctance or even distress.

The KardiaMobile 6L is a handheld ECG device. It offers a less intrusive way to take ECG measurements with less need for undressing and without using conductive gel. This benefit may be particularly relevant for people with acute psychosis or mania who may find traditional ECG measurement challenging but is also helpful for people who may be uncomfortable undressing for the test. KardiaMobile 6L ECG can be recorded during a routine home visit by a community health professional, and the results emailed to the person's clinical team. This may reduce stress and anxiety because the test can be done in familiar surroundings.

This topic is presented as an early value assessment. The decision question that would need to be answered in guidance is presented below. This early value assessment aims to map the available evidence against this decision question to understand the evidence gaps that may need to be filled.

Decision question

Does using KardiaMobile 6L for measuring QT interval in adults having antipsychotic medication represent a clinical- and cost-effective use of NHS resources?

Populations

The populations in this assessment are:

- adults who should be offered an ECG before starting antipsychotic medication
- adults taking antipsychotic medication who need an ECG to monitor QT interval.

Depending on the availability of evidence, condition-specific subpopulations including people with psychosis and schizophrenia, bipolar disorder, dementia or depression may be considered.

Interventions

KardiaMobile 6L (AliveCor) 6-lead ECG device.

Comparator

12-lead ECG device.

Healthcare setting

- Community (people's homes or care homes)
- Primary care (GP, primary care centres or rehabilitation centres)
- Psychiatric inpatient facilities
- Psychiatric outpatient clinics (including community mental health teams).

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope for KardiaMobile 6L for measuring QT interval in people having antipsychotic medication.

2 Evidence summary

Clinical effectiveness

Limited evidence was found. There are 8 published studies that evaluated the technical performance of KardiaMobile 6L compared with a 12-lead device. None of these studies included people having antipsychotic medication and the ECGs were interpreted by 1 or more cardiologists rather than a healthcare professional such as a psychiatrist or psychiatric nurse likely to record an ECG in a psychiatric service setting. The mean difference in QTc between the 12-lead ECG and KardiaMobile 6L was generally small. But the apparent direction of the difference suggested that KardiaMobile 6L consistently underestimated the length of the QT interval. It was not clear if the differences in measured QTc would have led to different clinical care for people. No published study or the NHS pilots reported on clinical outcomes or health-related quality of life.

In a recent NHS pilot project in people having antipsychotic medication, service users found having an ECG with KardiaMobile 6L more comfortable than with the traditional 12-lead device. They found KardiaMobile 6L easier to use than a 12-lead device, preferred it for dignity and privacy, and considered 12-lead ECG to be more intrusive than KardiaMobile 6L.

Further details are in the Clinical effectiveness evidenceClinical effectiveness evidence

Costs and resource use

No published economic evaluations on measuring QT interval in people having antipsychotic medication were found. A review of data sources available to inform modelling was done.

Key parameters that were identified as relevant for future economic modelling which had data available included:

- the pay band of the healthcare professionals recording the ECG,
- staff training time,
- time to record an ECG,
- time to interpret an ECG locally,
- requests for ECG interpretation centrally,
- technical failure rate,
- the proportion of KardiaMobile 6L ECGs needing a follow-up 12-lead ECG,
- device and training costs, and
- the costs of recording and interpreting the ECG.

The parameter values were informed by very limited data sources and so they are uncertain. While most estimated parameter values were similar for both KardiaMobile 6L and the 12-lead device, the cost of the KardiaMobile 6L was much lower than the cost of the 12-lead device. The estimates of time to record an ECG suggested it was faster to use KardiaMobile 6L than 12-lead device. But these estimates varied greatly. They were not all directly measured and [redacted] So, it was not certain whether using KardiaMobile 6L would save time.

For some parameters, no estimated values were found. These included the number of people referred for an ECG before starting antipsychotic medication, time from ECG result to starting antipsychotic medication, the number of ECGs recorded in people having antipsychotic medication, antipsychotic drug use (drug and dose) and attendance rates for KardiaMobile 6L and 12-lead device ECG appointments.

[redacted]

[redacted]

Further details are in the Resource use and costs section.

3 Clinical effectiveness evidence

An external assessment group (EAG), Kleijnen Systematic Reviews, did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of KardiaMobile 6L for measuring QT interval in people having antipsychotic medication. Find the full review methods and results on pages 19 to 70 of the early value assessment report.

Overview of included studies

The systematic review included 8 studies reported in 13 peer-reviewed publications and 2 unpublished reports.

Of the published studies, 5 observational technical validation studies, 2 pilot studies and 1 case series study evaluated the technical performance of KardiaMobile 6L. The 2 unpublished reports reported regional data from a wider NHS pilot project that was not done as formal research. All the published studies were prospective. The unpublished pilot projects collected data retrospectively. Two of the published studies and the 2 unpublished pilot projects were done in the UK. Other studies were done elsewhere in Europe, US and Australia.

Find an overview of the included studies in table 2 on pages 38 to 44 of the early value assessment report.

Study quality

The EAG assessed the quality of the 5 technical validation studies using elements of the QUADAS-2 tool, which is designed for diagnostic accuracy

studies. The risk of bias in these studies was mostly low or unclear. But, for all studies, there was high concern over the applicability of the population to the decision question in this assessment. This was because none of the studies included people having antipsychotic medication. Instead, the studies reported data from people referred to cardiology and genetic heart rhythm clinic, healthy athletes and in people who were in the healthy control group in a COVID-19 study. There was also a high concern over the applicability of the index test to the decision question in this assessment. This was because, instead of a nurse or other health professional likely to interpret the ECG for people having antipsychotic medication, the ECGs were interpreted by 1 or more cardiologists. Find a summary of the QUADAS-2 assessment in table 3 on page 49 of the early value assessment report.

No formal tool was available to assess the quality of other study types. Instead, the EAG described the key issues in the 2 unpublished NHS pilot projects with respect to reliability of the information they provide to address the decision question in this assessment. [redacted]

Intermediate outcomes

Technical performance

Table 1 summarises the estimates of agreement between heart rate corrected QT interval (QTc) measured by 12-lead ECG and by KardiaMobile 6L in the 8

studies that evaluated technical performance. QTc is considered normal if below 440 milliseconds (ms) for men, or below 470 ms for women. Only 1 study (Azram et al. 2021) separately reported QT interval measured using ECG output from lead II, one of the 2 leads recommended by the British Heart Rhythm Society clinical practice guidelines available in both devices. In the rest of the studies, it was unclear if lead II had been used for all measurements or at all. The mean difference in QTc between the measurements was generally small (at most 10 ms) with KardiaMobile 6L estimating a slightly shorter QT interval than 12-lead ECG. But 1 study (Kleiman et al. 2021) reported that the absolute difference in QTc was 10 ms or more in 56% and 40 ms or more in 5% of the 671 people who had an ECG recorded using both devices. Overall, there was no information on whether the generally small difference in QT interval would have led to different clinical follow up for any of the people enrolled in the study. No study reported data to calculate the diagnostic accuracy of KardiaMobile 6L in detecting QT prolongation. Find more details in table 5 on pages 56 to 60 of the early value assessment report.

Of these 8 studies, 1 (Azram et al. 2021) reported that QT interval could be measured from lead II in 73% of people using KardiaMobile 6L and in 77% of people using the 12-lead device. One further study (Minguito-Carazo et al. 2021) reported that QTc could be measured by KardiaMobile 6L lead II in 91% of the cases. In addition to these published studies, the unpublished pilot study from the Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust provided some information about technical failures. During the pilot, healthcare professionals using KardiaMobile 6L submitted 42 support tickets with 15 clinical and 27 technical queries. Of the technical queries, 2 were about the device and the remaining 25 were about either the KardiaMobile app or Microsoft Outlook.

Table 1 Agreement between corrected QT interval measured by 12-lead ECG and KardiaMobile 6L

Study	Study size using KardiaMobile 6L, using 12-lead ECG	Mean QTc using KardiaMobile 6L in ms (standard deviation)	Mean QTc using 12-lead ECG in ms (standard deviation)	Mean difference in QTc in ms
Azram et al. (2021)	72.8% of 1,1015, 76.6% of 1,1015	Not reported	Not reported	1 (lower limit of agreement -52, upper limit of agreement 53)
Frisch et al. (2021)	7, 8	460 (30)	464 (19)	4 (95% CI -22 to 30)
Kleiman et al. (2021)	671, 674	429 (37)	431 (39)	3 (95% CI -2 to 7)
Krzowski et al. (2021)	97, 98	366 (not reported)	403 (not reported)	Not possible to calculate
Minguito-Carazo et al. (2021)	45, 45	409 (23)	412 (28)	3 (95% CI -8 to 23)
Orchard et al. (2021)	30, 30	391 (24)	401 (25)	10 (95% CI -2 to 22)
Puranik et al. (2022)	13, 13	Not reported	Not reported	3% mean percentage difference between automated 12-lead and manually calculated KardiaMobile 6L readings (largest percentage difference 12%)
Shah et al. (2021)	3, 3	423 (not reported, participant 1) 417 (not reported, participant 2) 430 (not reported, participant 3)	420 (not reported, participant 1) 419 (not reported, participant 2) 422 (not reported, participant 3)	-3 (participant 1) 2 (participant 2) -8 (participant 3)

[redacted]

In the Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust pilot, 9 of 16 healthcare professionals said a follow-up 12-lead ECG was needed after using KardiaMobile 6L. This was because of poor readings due to movement or lack of contact between skin and electrodes, need for more information for clinical decision making, need for follow-up monitoring, and an abnormal ECG result.

Clinical outcomes

None of the published studies reported on clinical outcomes. [redacted]

Health-related quality of life outcomes

No study reported on health-related quality of life outcomes.

Service user and healthcare professional preferences

[redacted]

In the Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust survey, all 33 service user respondents thought having an ECG with

KardiaMobile 6L was more comfortable than with the traditional 12-lead device. Nearly all said KardiaMobile 6L was easier to use than the 12-lead device, preferred KardiaMobile 6L dignity and privacy, and considered 12-lead ECG to be more intrusive than KardiaMobile 6L. Nearly all had an overall preference for KardiaMobile 6L and said they would prefer KardiaMobile 6L for future monitoring, but the EAG cautioned that the participants were not given any information on the accuracy of both 6-lead and 12-lead. Healthcare professional respondents' preferences were similar, except the proportion who considered 12-lead ECG less intrusive than KardiaMobile 6L and those who indicated an overall preference for KardiaMobile 6L was slightly smaller. Of the 51 respondents, 40 said it was easier to send test information to the relevant healthcare professional using KardiaMobile 6L.

[redacted]

Ongoing studies

The EAG identified 4 potentially relevant ongoing technical or clinical validation studies. One of these aims to evaluate safety and clinical utility of handheld ECG technology (AliveCor) in psychiatry in the Leeds and York Partnership NHS Foundation Trust. Find more details in appendix 4 of the early value assessment report.

4 Resource use and costs

Systematic review of cost-effectiveness evidence

The EAG's systematic review also aimed to identify published economic evaluations of measuring QT interval by any ECG method in people having antipsychotic medication. No such studies were found.

Resource use

The EAG's review, and a supplementary report from KiTEC that contained a rapid scoping review, looked for information on resource use and costs associated with using either KardiaMobile 6L or the traditional 12-lead ECG to measure QT interval in people having antipsychotic medication.

In addition to technical failure rate and the proportion of KardiaMobile 6L ECGs needing a follow-up 12-lead ECG (see section on technical performance), relevant resource parameters for which value estimates were found included the pay band of the healthcare professionals recording the ECG, staff training time, time to record an ECG, time to interpret an ECG locally, and requests for ECG interpretation centrally. Table 2 presents the estimated parameters. Multiple sources provided estimates of time to record an ECG but these varied greatly. The rest of the parameter estimates for both devices were similar. Find more details on pages 13 to 18 of the cost and resource use report.

One technical validation study (Minguito-Carazo et al. 2021) and [redacted] Find more details in table 7 on page 66 of the early value assessment report.

Table 2 Resource use associated with using 12-lead ECG and KardiaMobile 6L to measure QT interval in people having antipsychotic medication

Resource parameter	12-lead ECG	Kardiamobile 6L	Sources
Pay band of the healthcare professionals recording the ECG	Band 3 and 6	Band 3 and 6	CNTW NHS Foundation Trust (2021)
Staff training time	2 to 3 hours	2 training sessions (length not known)	Expert opinion and CNTW NHS Foundation Trust (2021)
Time to record ECG	Estimates varied from 4 minutes to 25 minutes excluding travel time (or 45 minutes including travel time)	Estimates varied from 1 minute to 8 minutes excluding travel time (or 24 minutes including travel time)	Minguito-Carazo et al. (2021), CNTW NHS Foundation Trust (2021), Cancer Research UK (2022, source study unclear), Foster et al. 1994) and expert opinion
Time to interpret ECG locally	4 minutes	4 minutes	CNTW NHS Foundation Trust (2021)
Requests for ECG interpretation centrally (cardiology)	20% of GP practices used secondary care to report all or some of their ECGs (this proportion was 65% for GP practices which referred people for an ECG elsewhere)	Data not found	Wolff et al. (2012)

Parameters that would be relevant but for which no data was found included the number of people referred for an ECG before starting antipsychotic

medication, time from ECG result to starting antipsychotic medication, the number of ECGs recorded in people having antipsychotic medication, attendance rates for KardiaMobile 6L and 12-lead device ECG appointments and medication use.

Costs

KiTEC identified that both the 12-lead ECG and the KardiaMobile 6L would be associated with device and training costs, and the costs of recording and interpreting the ECG. Table 3 presents the estimated costs. The cost of the 12-lead ECG device was substantially higher than the cost of the KardiaMobile 6L device. The rest of the unit costs associated with using the devices were similar. Find more details on pages 19, 22 and 33 of the cost and resource use report.

Table 3 Costs associated with using 12-lead ECG and KardiaMobile 6L to measure QT interval in people having antipsychotic medication

Cost parameter	12-lead ECG	KardiaMobile 6L	Sources
Device and accessories	£2,231	£965 (includes an iPad and a 1-year renewable license cost)	AliveCor; CNTW NHS Foundation Trust (2021); NICE guideline for preoperative tests for elective surgery (NG45)
Training (by a band 3 or band 6 nurse)	£153 (hospital) or £165 (community)	Not estimated (not enough information)	PSSRU Unit Costs of Health and Social Care 2021
Recording of ECG (by a band 3 or band 6 nurse)	£27 or £51 (hospital), or £26 or £55 (community)	£26 or £55 (community)	PSSRU Unit Costs of Health and Social Care 2017 and 2021
ECG interpretation	£1 to £2 (locally) or £17 (centrally by private provider)	£1 to £2 (locally) or £17 (centrally by private provider)	British Medical Association 2022 pay scales; CNTW NHS Foundation Trust (2021)
Cost of cardiology follow-up	£142	£142	2019/2020 NHS reference cost

The EAG also noted that the reports from the 2 unpublished NHS pilot projects also included some cost estimates. [redacted]

The Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust pilot estimated that if a band 3 healthcare professional used KardiaMobile 6L to record an ECG, the cost was about £2.40 less compared with an ECG recorded using a 12-lead ECG. This estimate seemed to have been calculated based on the healthcare professionals' responses to the survey done as part of the evaluation.

The Cumbria, Northumberland and Tyne and Wear NHS Foundation Trust pilot from Cumbria also estimated yearly ECG costs with KardiaMobile 6L ECGs interpreted locally and 12-lead ECGs interpreted either locally or by a centralised service by a private provider. Based on these estimates, Kleijnen calculated that using KardiaMobile 6L would save over £3,000 per year if all 12-lead ECGs were interpreted locally, and over £7,000 per year if all 12-lead ECGs were interpreted using the centralised service. But considering the added costs of 60% of all KardiaMobile 6L ECGs needing a follow-up 12-lead ECG, using KardiaMobile 6L would save only about £125 per year if all 12-lead ECGs were interpreted locally and £700 per year if all 12-lead ECGs

were interpreted centrally. Find more details on pages 67 and 68 and in table 8 on page 70 of the early value assessment report.

5 Issues for consideration

Clinical effectiveness

One of the recent NHS pilots where KardiaMobile 6L was used in people having antipsychotic medication included survey data on service user satisfaction. It is unclear whether this survey captured all subgroups whose views should be considered such as people who may find it challenging to sit still, or have physical or cognitive impairment. Is a wider survey needed?

The technical validation studies suggested that the difference in the length of QT interval between the 12-lead ECG and KardiaMobile 6L was generally small, but it is unclear if the difference would affect treatment decisions. Because none of these studies included people having antipsychotic medication and the ECGs were interpreted by 1 or more cardiologists rather than a healthcare professional such as a nurse or psychiatrist who are likely to record an ECG in a psychiatric service, it is uncertain whether the performance reported in the technical validation studies would be seen in practice in measuring QT interval in people having antipsychotic medication. There were no studies that reported the diagnostic accuracy of KardiaMobile 6L for measuring QT interval. Is data on the accuracy of KardiaMobile 6L for measuring QT interval in people having antipsychotic medication needed before the device can be used in the NHS alongside data collection?

There was no data on treatment decisions, psychiatric or cardiac outcomes or health-related quality of life. Would data on treatment decisions be enough to allow for linked evidence modelling in the future? Or is data on longer-term clinical outcomes and health-related quality of life needed to assess the clinical effectiveness of KardiaMobile 6L for measuring QT interval?

Cost and resource use

[redacted] It is not certain whether using KardiaMobile 6L would result in cost savings. But does using KardiaMobile 6L to measure QT interval in people having antipsychotic medication have the potential to be cost effective?

The resource parameters with uncertain values or for which no values were found included:

- number of people referred for an ECG before starting antipsychotic medication
- pay band of the healthcare professionals recording the ECG
- staff training time
- time to record an ECG
- technical failure rate
- time to interpret an ECG locally
- number of requests for ECG interpretation centrally
- time from ECG result to starting antipsychotic medication
- number of ECGs recorded in people having antipsychotic medication
- attendance rates for KardiaMobile 6L and 12-lead device ECG appointments
- medication use.

The cost parameters with uncertain values or for which no values were found included:

- training costs
- cost of recording ECG

- cost of interpreting ECG.

Are there any other relevant resource or cost parameters relevant for future economic modelling for which data should be collected?

Are there any parameters which could be informed by already collected real world data such as electronic health record data or observational real-world studies?

6 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

KardiaMobile 6L may not be suitable for use for people with upper limb amputation or missing fingers. The accuracy of readings may be adversely affected if a person has a skin condition causing irritation, inflammation, or very dry skin. The devices may not work correctly for people with a pacemaker or implantable defibrillator. Readings from people with tremors or those who find it challenging to sit still may also be inaccurate. The KardiaMobile 6L has not been tested for and is not intended for paediatric use.

A 12-lead device uses torso electrodes and needs people to undress for the ECG. People should be asked to remove only clothing preventing access to the correct electrode positions. A chaperone may be requested for appointments using these devices. But people may be uncomfortable with undressing for example because of culture or religion, the gender of the ECG operator, or because they have a different gender identity to their birth sex, history of trauma or sexual abuse, or they experience hyper-sensitivity, for example as part of autism spectrum disorder. Because of the torso electrodes,

body hair may need shaving for adequate contact with the skin before the ECG.

People from minority ethnic backgrounds, particularly people of African and African-Caribbean family background living in the UK, are more likely than white British people to be diagnosed with schizophrenia. They are also more likely to be detained, given medication against their will, or given higher doses.

Neurodiverse people (for example people with autism spectrum disorder) may be more likely to have antipsychotic medication than the general population.

Antipsychotic medication is likely to be given to people affected by postpartum psychosis. ECG testing may be appropriate for this population before starting treatment.

Women typically have a longer QT interval than men and therefore may be more susceptible to the effects of QT-prolonging medication. Different QTc thresholds may be used for men and women.

7 Implementation

Data transfer and protection

KardiaMobile 6L needs to connect to the internet to transmit ECG data to clinicians. This may not be possible for some home visits. If not done correctly, the ability to save and send information could be a risk to data protection and information governance. Companies have stated that they have appropriate systems in place to ensure the devices and software are compliant with the relevant policies and law. Devices may need digital technology assessment criteria (DTAC) approval before use in the NHS.

8 Authors

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Glossary

Corrected QT interval (QTc)

To be able to compare measurements at different time points and at different heart rates, the QT interval is corrected for heart rate. Corrected QT interval is used for clinical decision-making.

ECG lead

An ECG lead is a graphical representation of the heart's electrical activity which is calculated by analysing data from 1 or 2 ECG electrodes.

The 6 leads recorded by KardiaMobile 6L are:

- lead I – lateral view between right arm and left arm electrodes.
- lead II – inferior view between right arm and left leg electrodes.
- lead III – inferior view between left arm and left leg electrodes.
- aVR – calculated by analysing activity between the sum of the left arm and left leg electrodes and the right arm electrode.
- aVL – calculated by analysing activity between the sum of the right arm and left leg electrodes and the left arm electrode.
- aVF – calculated by analysing activity between the sum of the right arm and left arm electrodes and the left leg electrode.

The leads V1 to V6 are calculated using activity from electrodes placed on the surface of the torso using 12-lead device. These are not available when using the KardiaMobile 6L.

QT interval

QT interval is the time between the beginning of the Q wave and the end of the T wave in an ECG. It represents the time taken for the ventricles of the heart to depolarise and then repolarise. 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.

NICE National Institute for Health and Care Excellence

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Early Value Assessment Report - Comments

Comments on the Early Value Assessment Report

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
AliveCor	1	16	Plain English Summary	This paragraph is factually incorrect. "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." It should be corrected to: KardiaMobile 6L (or 6-lead) is a portable ECG that 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 fingers of the left and right hand and the left ankle or knee and the cold gel is not needed.	The text has been corrected to: ' This is because less undressing is needed since the electrodes are only applied to fingers of the left and right hand and the left ankle or knee and the cold gel is not needed.'
AliveCor	2	22	2.2	This paragraph is factually incorrect. "It uses three electrodes to record a person's ECG and wirelessly transmits the data in a portable document format (PDF) to a compatible smartphone or tablet via Bluetooth." It should be corrected to: It uses three electrodes to record a person's ECG and wirelessly transmits the data to a compatible smartphone or tablet via Bluetooth. The Kardia application allows the ECG data to be converted into a portable document format (PDF).	This correction has been made.
AliveCor	3	23	2.2	As per our IFU, DO NOT use KardiaMobile6L with patients who have a cardiac pacemaker, ICDs, or other implanted electronic devices.	This infromatioin has been added to section 2.2 or our report.
AliveCor	4	14	Results	"However, it should be noted that none of the included studies provided any information to indicate in how many (if any) patients observed differences in measured QTc would have resulted in a change of clinical category" Please consider: • Gonzalez NT, et al. QT interval measurement with portable device during COVID-19 outbreak.IJC Heart & Vasculature.2020:30. From search protocols,we are unsure why this would have been excluded.	This study does not meet the iclusion criteria for the current assessment, because: 1. It does not provide any comparison with 12-lead ECG, it is a retrospective study reporting the use of KardiaMobile to motitor QTc interval in COVID-19 patients 2. The study does reference an earlier validation study, comparing KardiaMobile to 'QTc interval measured in

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Early Value Assessment Report - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					lead V5 of conventional body surface ECG.' However, both the Gonzalez study and the earlier validation study used KardiaMobile 6L in the single lead mode and hence do not meet inclusion criteria for the intervention, as specified for this assessment.
AliveCor	5	79	Implications for service provision	"...it remains unclear whether KardiaMobile 6L has adequately demonstrated sufficient evidence of potential advantage(s) over current practice to justify further research to inform assessment of its clinical and cost effectiveness." Additional research would be looking for clinical equivalence. In order to show advantages, this data would only come from studies of user preference, cost, and/or time. The assessment would not look for clinical superiority, correct?	We are not entirely clear what is being asked, however, to summarise, what is needed for an assessment of clinical and cost effectiveness is, broadly: 1. Evidence about the either the clinical effects of KardiaMobile 6L compared to 12-lead ECG, or evidence about the clinical accuracy of KardiaMobile 6L for detecting clinically relevant QT prolongation, where 12-lead ECG is the reference standard AND 2. Evidence about the proposed advantages of KardiaMobile 6L (user acceptability, costs, time, etc) With regards to expectations of clinical superiortity or equivalence, that depends on the comparator i.e. no ECG or 12-lead ECG as well as the naure of the clinical outcome

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Early Value Assessment Report - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					e.g. KardiaMobile 6L might be expected to be no more accurate than 12-lead ECG, but reducing time to testing might improve clincial outcomes. Evidence needs to be for the population in which the device is being evaluated. This is because, although the target condition (QT prolongation) may be the same across different populations, the clinical performance of KardiaMobile 6L is likely to vary with, for example, the type of patients in which it is used (e.g. how still can/does the 'average' patient remain), who is using the device and the setting in which it is being used.
AliveCor	6	79	Suggested research priorities	Would a retrospective study of KardiaMobile 6L used in representative populations of service users who require antipsychotic medication and the ECG examinations read by healthcare providers who are representative of those who would be expected to undertake the examination in real world clinical practice which includes clinical outcomes by patient and technical failure rates be sufficient evidence to support use in this population, if the study was taken in combination with the numerous technical validation studies which already show correlation with 12-lead?	This a matter for the committee to decide. However, the ERG do not consider that such a study would be adequate, as it would not provide any means of comparing the clinical efficacy of KardiaMobile 6L to current practice (either directly, or using a linked evidence approach). As explained in our report, technical validation studies cannot provide any information about how many patients with the target condition may be missed (false negatives) if the technology were implemented. This is a function of the study design, technical validation (correlation of measurements between devices) is not the same as clinical validation (determining

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Early Value Assessment Report - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					whether a device performs adequately to detect the target condition at a pre-defined clinical threshold, when used as it would be in clinical practice).
AliveCor	7	68	4.6	"KardiaMobile 6L = £1, 542.19 – based on ECG readings taken by a Band 3 staff member and local manual interpretation by a doctor in training/CNTW staff member, and including device costs (including iPad and licences)" There are no licences associated to KardiaMobile what are the economics here associated to licences?	This is information taken from the CNTW project report and we are not clear what, exactly was meant by 'licences'; this could be in relation to the iPad, rather than KardiaMobile 6L itself.
AliveCor	8	4	Methods	"We did not identify any studies which provided information about the diagnostic accuracy of KardiaMobile 6L, for the detection of QTc-interval prolongation, in any population." The sentence in the report contradicts and qualifies this in saying that there are no psychiatric population studies but "drug-induced QT prolongation does not differ whether the drug is an antipsychotic, methadone, antibiotic, cancer or cardiac drug so the multiple validation studies of the use of the Kardia 6L for QT assessment in other populations are directly applicable to this problem."	We are unclear what point is being made here. As stated in the report, We did not identify any studies which provided information about the diagnostic accuracy of KardiaMobile 6L, for the detection of QTc-interval prolongation, in any population.'' Hence, in the context of this report, the value or otherwise of accuracy data obtained in different populations is a moot point. As explained in our report and in response to comment 6, above, technical validation studies are critically different from clinical accuracy studies and technical validation cannot provide a substitute for clinical accuracy data. Further, as detailed in our response to comment 5, it is important to obtain clinical accuracy data in the correct population in order to capture all factors that may effect the performance/clinical accuracy of the device.

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Early Value Assessment Report - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
AliveCor	9	5	Methods	A difference of less than 10msec between a Kardia 6L and 12-lead ECG QT measurement is insignificant when looking at the vast QT literature.They are essentially the same.	Interpretation - results were reported as observed. No change needed.
AliveCor	10	5	Conclusion	The psychiatric use of the Kardia 6L is no different than its use for evaluating drug-induced QT prolongation of any drug and there are a number of published studies which validate the clinical application in cardiac and other patients.	The ERG does not consider that all intended applications of KardiaMobile 6L (or any test or device) should be assumed to be 'no different', as there are many population and setting related factors that can affect the performance of a test or device. In addtition, as stated in our report, whilst there are a number of technical validation studies of QTc measurement using KardiaMobile 6L, we have not identified any clinical accuracy studies and AliveCor have not provided any such studies.
College of Mental Health Pharmacy	11			Overall comment of report; in agreement with conclusions, no specific comments to add. In practice, carrying out an ECG can introduce delays to treatment, but actually the majority of patients who would require a pre-treatment ECG (as per NICE recommendations) are an inpatient with easy access to a 12-lead ECG.	No response required.

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KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Cost and Resources Report - Comments

Comments on the Cost and Resources Report

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAC response
AliveCor	1	9		"Staff found that despite the longer time required to take a 12L ECG (30 seconds for a KardiaMobile device versus 60 seconds for a 12L ECG), when patients were agitated and restless the 12L ECG outperformed the KardiaMobile device as it was able to obtain clearer readings." We understand this statement to be in accurate, the poster presented by The Tees Remote ECG Pathway portrays this very differently also from a patient perspective of 12L ECG vs KM6L	This is informed by qualitative evidence from the Kardiamobile Pilot Study (2021), on when a 12-lead ECG was preferred or required following a 6-lead KardiaMobile ECG. "Patient could not maintain contact with both hands and knee for full 30 seconds, following place meant of ECG electrodes patient allowed to rest on bed once relaxed ECG recorded. Longer to record but more clear reading from 12Lead"? (Kardiamobile Pilot Study (2021) page 48) "Unsettled or agitated patients, or those with a tremor, who are unable to remain still for the 30 seconds necessary to obtain a decent trace" (Kardiamobile Pilot Study (20121) page 45) We also note that the presented information is coherent with information in the systematic review by Kleijnen Systematic Reviews Ltd ("Where a specific reason was given for non-completion of an ECG, the most common reported reasons were [redacted] specifically, that the patient was [redacted]

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Cost and Resources Report - Comments

					[redacted] in [redacted] of instances", page 77).
AliveCor	2	22	3.12	"It should be noted that this does not account for ongoing licence costs (£73.87 per year)," There are no licences associated to KardiaMobile what are the economics here associated to licences?	The licenes fees refer to E1 and security licences for the use of iPads, as reported in the KardiaMobile Pilot Study (2021). This reflects the required setup costs to use the KardiaMobile 6L. "The KardiaMobile Pilot Study (2021) further reports that each iPad costs £742 and the E1 and security licence for each iPad cost £73.87 and required renewal on an annual basis."
AliveCor	3			Inconsistency between documents: Figure 2 Cost and Resources report differs significantly from the External Assessment report (in which cases to take a 12 lead ECG)	To clarify, Figure 2 was adapted from the guidelines for the Management Of QTc Prolongation in Adults Prescribed Antipsychotics (see report page 7) and informed by clinical experts collectively. Assuming this comment refers to the decision concerning whether a 12-lead ECG may be required to confirm the outcome of the 6-lead ECG, we did not identify any inconsistency between Figure 2 and the content of the EAR. In fact, referring to quotes from the report: "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, this would be the case both for both assessment prior to the initiation of antipsychotic

KardiaMobile 6L for measuring QT interval in people having antipsychotic medication

Cost and Resources Report - Comments

					medications and for monitoring QT interval-based cardiac risk once medication has been established. 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." (EAR page 12) "A 12-lead ECG maybe required in cases where the outcome of the 6L device is unclear,or if other heart conditions such as ischaemia or left ventricular hypertrophy are suspected" (EAR page 23) "two responses indicated that the KardiaMobile6L result had been used to rule out heart abnormalities, and indicated that a 12-lead ECG was still needed" (EAR page 61)