Validation of a smartphone-based Recorder for Detection of Cardiac arrhythmias

Principal Investigator:

Sub-Investigators:

Research Trust: Blackpool Teaching Hospitals NHS Foundation Trust

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1 Study Summary

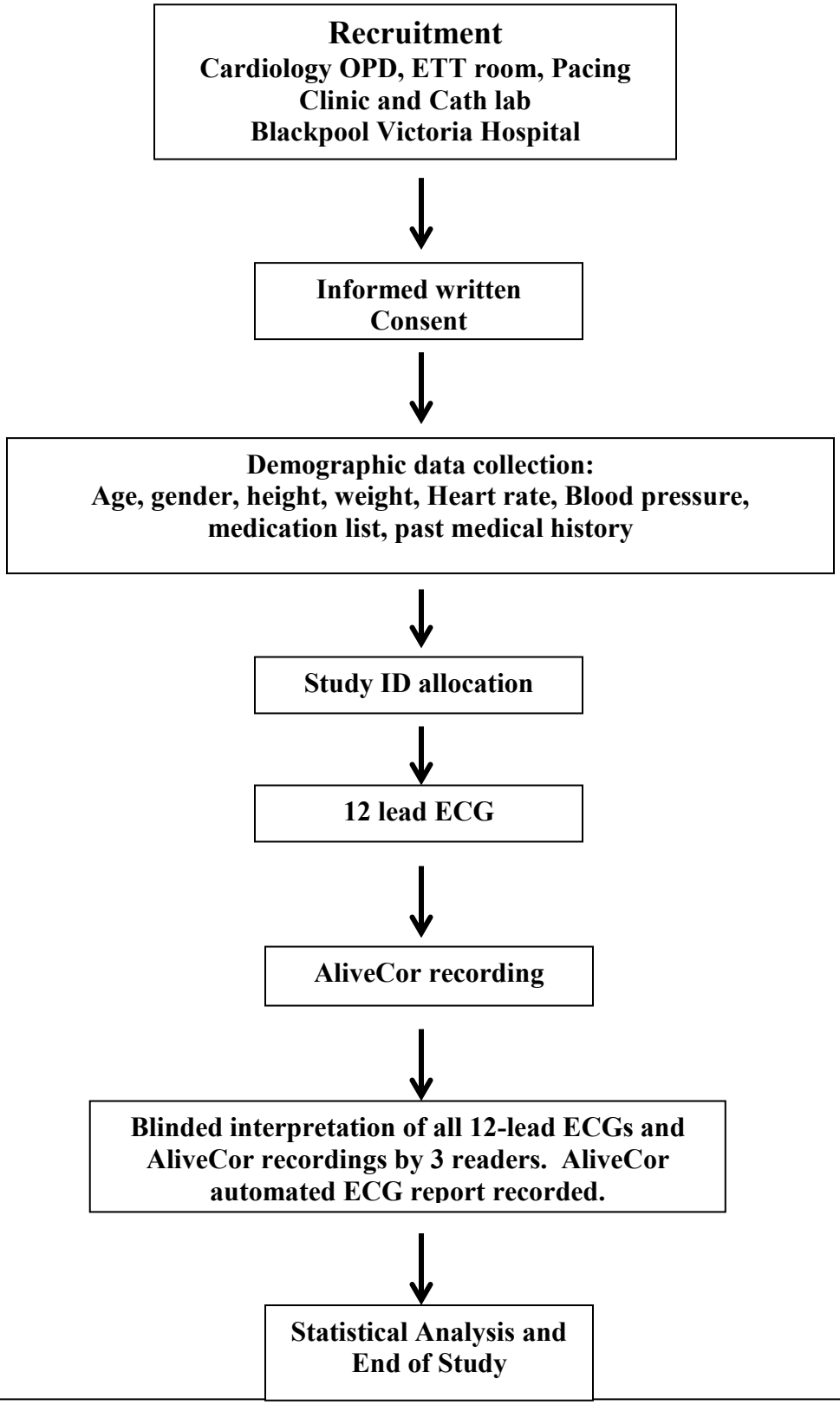
Title	Validation of a smartphone-based Recorder for Detection of Cardiac arrhythmia
Short Title	Validation of AliveCor system for Detection of Cardiac arrhythmia
Version & Date	Version4a-AC-27072018
Principal Investigator	Dr Khalid Abozguia
Sub-Investigators	Dr Gavin Galasko, Dr Hossamaldin Abuomara.
Objectives	We will evaluate the diagnostic yield of the new AliveCor device versus a 12 lead ECG when used simultaneously to detect cardiac arrhythmia
Methodology / Design	Non-randomised open label diagnostic study We are planning to record 250 pre-defined abnormal ECGs (50 each of atrial fibrillation, atrial flutter, pre-excitation, ventricular tachycardia, , supraventricular tachycardia) and 150 control ECGs (100 sinus rhythm, 50 sinus tachycardia) using both the AliveCor Smartphone device and a 12-lead ECG. All 400 ECGs will then be read by 3 blinded reporters – a Consultant Electrophysiologist, a Consultant General Cardiologist and a General Practitioner. The output of the AliveCor automatic detection algorithm will also be recorded as a fourth reporter. The screening characteristics of all 4 reporters using the AliveCor device *vs* the definitive 12 lead ECG will be analysed and compared. Patients can be recruited from different cardiology clinics; at the end of an exercise test to record sinus tachycardia, and in the catheter lab during electrophysiological studies/ ablation procedures to record arrhythmias. Every patient will be counselled about the project by a member of the cardiology / research team (doctor or qualified research nurse) and will be provided with a patient information sheet. Patients will be given up to 2 weeks to consider participation in the study. If in agreement, written informed consent will be obtained. A 30-second ECG tracing will be obtained by simply holding the Smartphone and placing at least 1 finger from each hand on electrodes embedded into the back of the Smartphone case (figure 2). For sedated patients in the catheter lab, AliveCor electrodes will be placed and taped on patient chest wall, left parasternal third intercostal space. The AliveCor ECG tracing will be recorded as close to simultaneously as the 12 lead ECG

	recording as possible.
Duration	2 years
Participating Centres	Blackpool Victoria Hospital
Primary End Point	Screening characteristics and diagnostic accuracy of AliveCor ECG recordings to detect cardiac arrhythmias
Number of participants	400
Main Inclusion /Exclusion Criteria	Inclusion: • Male or female patients >18 years with 12 lead ECG finding of arrhythmia, manifest pre-excitation, pacing rhythm, sinus rhythm or sinus tachycardia. Exclusion Criteria: • Patients <18 years of age. • Patients unable to or unwilling to use the device.

Statistical Methodology and Analysis	400 patients are planned to be recruited as follows: 50 patients with supraventricular tachycardia (SVT) 50 patients with atrial flutter (AFl) 50 patients with atrial fibrillation (AF) 50 patients with ventricular tachycardia (VT) 50 patients with manifest pre-excitation 50 patients with sinus tachycardia to constitute the tachycardia control group 100 normal ECGs will also be collected from the first 100 patients who have regular sinus rhythm to constitute the sinus rhythm control group. ECGs will be recorded in duplicate, with one recording being made using the AliveCor device, and one recording being made using a normal 12-lead ECG. Recordings will be undertaken as close to simultaneously as possible. The ECG diagnosis will be made by the lead Electrophysiologist on the 12-lead ECG so produced and this will be taken as the correct ECG diagnosis. All ECGs (both 12-lead and AliveCor) will be reported by a Consultant Electrophysiologist, a General Cardiologist and a General Practitioner, blinded to the full study protocol and the patient allocation group. The output of the AliveCor algorithm for automatic ECG diagnosis will also be recorded. The readers will firstly read the AliveCor ECGs and at a later date read the 12-lead ECGs to prevent comparisons between the ECGs and to give accurate screening characteristics for AliveCor ECGs. The diagnostic accuracy and screening characteristics of ECGs generated by the AliveCor device will be reported for each arrhythmia individually and in combination both by each reporter. To calculate screening characteristics, ECGs of sinus rhythm and sinus tachycardia will also be included in each analysis as normal controls. 95% confidence intervals will be calculated. The primary end-point will be the sensitivity and screening characteristics of detecting each arrhythmia individually and in combination by each reporter using the AliveCor device, calculating 95% confidence intervals. The binomial exact calculation would be used to calculate confidence intervals. With a sample size of 50 patients with one arrhythmia, a sensitivity of 80% would produce a 95% confidence interval of 68.9% to 91.1%. With a sample size of 250 (all arrhythmias combined), a sensitivity of 70% would produce a 95% confidence interval of 64.5% to 75.1%, i.e. an absolute error of ± 5%. The main secondary end-point will be to compare the sensitivity of a

	Consultant Electrophysiologist in detecting all arrhythmias using the AliveCor device *vs* the originally coded 12-lead ECG, to test whether the AliveCor device is non-inferior to the original 12-lead ECG diagnosis. Assuming a 95% one-sided confidence interval and a power of 80%, if there is a true difference in sensitivity in favour of the 12-lead ECG over an AliveCor ECG of 10%, and then a sample size of 301 would be needed to exclude a difference in favour of the 12-lead ECG of more than 16%. Further secondary end-points will be to compare a Consultant Electrophysiologist with a General Consultant Cardiologist with a General Practitioner and with the automated AliveCor ECG diagnosis using their automatic algorithm.

1.1 Flowchart of Treatment Schedule



2 Introduction

This is non-invasive diagnostic study. It is easily achievable and simple to conduct. If proven to be a positive study, this may potential be a cost-effective method to detect cardiac arrhythmia.

2.1 Background

In the past few years, the use of smart phones and tablets with health-related applications has significantly proliferated. AliveCor ECG (figure 1) is an FDA-approved, CE-marked portable electrocardiogram (ECG) recorder that records a single channel (lead I) ECG rhythm strip using a compatible smart phone running a specific application.[1,2] The recordings can be sent to a healthcare professional for interpretation. The healthcare professional accesses this information through the Provider Dashboard software.[3]

AliveCor Heart Monitor is an easy-to-use, highly-accessible, and cost-effective device which could be used to detect both paroxysmal and persistent arrhythmias in people who are asymptomatic as well as people with intermittent palpitations to determine the cause of their symptoms.

Figure 1

Description

The AliveCor Heart Monitor is a pocket-sized rectangular device containing 2 electrodes. Itis either attached directly via an adhesive attachment plate to a mobile device or must be within 30 cm of the mobile device during operation. The AliveCor Heart Monitor can be removed from the plate when not in use, with the plate remaining attached to the mobile device. The mobile device must be a standard internet-enabled mobile phone or tablet, onto which the AliveECG app must be downloaded. The AliveCor Heart Monitor and AliveECG app are compatible with devices running Apple or Android operating systems.[3]

How to use it?

To record an ECG, the user places 2 or more fingers from the left hand onto 1 of the AliveCor Heart Monitor electrodes and 2 or more fingers from the right hand onto the other electrode. The user keeps contact with the electrodes for at least 30 seconds to ensure that a complete reading is taken, while keeping their arms still because arm movement may interfere with the ECG reading.

After the AliveCor Heart Monitor has taken a reading, it is sent wirelessly by a patented high frequency sound transmission to the mobile device, where it can be viewed using the AliveECG (Kardia) app. If or when the device has a suitable Wi-Fi or mobile connection, the recording will automatically synchronise with the secure encrypted AliveCor cloud server. The user can also send the recording directly to a relevant healthcare professional, such as a GP, to be read using the Provider Dashboard, which is a web-based application run from any standard PC.[4,5]. For this study, we will only use trust enabled devices such as iPod/iPad available in Cardiology department- Cardiac Investigation Unit (CIU).

Cost:

The AliveCor system consists of an AliveCor Heart Monitor and the Kardia app. The AliveCor Heart Monitor costs £62.49, excluding VAT, for a single unit. For orders of 50 units or more, the price reduces to £50 each, excluding VAT. The Kardia app is available as a free download from the Apple App Store or from Google Play, and the web-based Provider Dashboard is free to use. The estimated cost of a standard 12-lead ECG, in which a practice nurse applies the test and a GP reviews the results, to be £36.33 with the cost of an ambulatory ECG as £170 (NICE 2014).[2]

Evidence from literature

- To date, the device has been used in current practice to improve the detection of recurrent AF [6] and to reliably monitor the QTc interval.[7]
- Lowres et al. (2014)[5] conducted a community-based, opportunistic screening programme of 1000 people aged 65 years and over, using the AliveCor Heart Monitor to detect AF. The study was set in 10 pharmacies in Sydney, Australia. Following the analysis of 996 readings, excluding 4 people with pacemakers, the AliveECG app had 98.5% sensitivity (67/68; 95% CI 92.1%–100%) and 91.4% specificity (849/929; 95% CI 89.4–93.1%), using the cardiologists' diagnosis from the AliveCor Heart Monitor reading as the reference case.
- The REHEARSE-AF (Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation) study is a randomized controlled trial of AF screening using an AliveCor Kardia monitor attached to a WiFi-enabled iPod to obtain ECGs (iECGs) in ambulatory patients. Patients ≥65 years of age with a CHADS-VASc score ≥2 free from AF were randomized to the iECG arm (500 individual) or routine care "RC" (501 individual). iECG participants acquired iECGs twice weekly over 12 months (plus additional iECGs if symptomatic) onto a secure study server with over read by an automated AF detection algorithm and by a cardiac physiologist and/ or consultant cardiologist. Time to diagnosis of AF was the primary outcome measure. The overall cost of the devices, ECG interpretation, and patient management were captured and used to generate the cost per AF diagnosis in iECG patients. Clinical events and patient attitudes/experience were also evaluated. Results showed that 19 patients in the iECG group were diagnosed with AF over the 12-month study period versus 5 in the RC arm (hazard ratio, 3.9; 95% confidence interval=1.4–10.4; *P*=0.007) at a cost per AF diagnosis of $10 780 (£8255). There was a similar number of stroke/transient ischemic attack/systemic embolic events (6 versus 10, iECG versus RC; hazard ratio=0.61; 95% confidence interval=0.22–1.69; *P*=0.34). The study concluded that screening with twice-weekly single-lead iECG with remote interpretation in

ambulatory patients ≥65 years of age at increased risk of stroke is significantly more likely to identify incident AF than RC over a 12-month period.[8]

- The iPhone Helping Evaluate Atrial Fibrillation Rhythm Through Technology (iHEART) [9] is an ongoing trial recruiting a total of 300 patients with a history of AF, with 150 patients receiving an iPhone with the mobile monitoring device and educational text messaging) the AilveCor system) and the remaining 150 patients continuing with their regular medical care. Each patient will be included in the intervention period for 6 months. The rate of recurrent AF and treatments meant to manage AF and other heart conditions will be determined for both groups. Patients in both groups will complete a series of questionnaires at the start and end of the 6-months study period to look at differences in quality of life and knowledge of AF.

Expected benefit:

The AliveCor Heart Monitor could be used in primary care as an alternative to other portable ECGs recorders to detect paroxysmal arrhythmias. There are several different portable ECGs available to the NHS. These devices, and the number of people in England who were monitored using these devices in 2013–14 following an outpatient appointment, are listed below (Health & Social Care Information Centre 2015) :[10]

- ECG loop recorder – 63 people
- 24-hour ambulatory ECG – 80,264 people
- 48-hour ambulatory ECG – 2863 people
- Holter extended ECG – 7186 people
- Cardiomemo ECG monitor – 4973 people.

Given that the mean cost of ambulatory ECG monitoring is £170, the adoption of the AliveCor may produce savings to the NHS.

Why we are conducting this study?

There are no validated studies to evaluate its use in arrhythmias other than AF.

2.2 Study Objectives

Primary objectives: To assess the sensitivity and screening characteristics of AliveCor recording to detect a wide range of cardiac arrhythmias (AF, atrial flutter, SVT, VT, paced rhythm and pre-excitation) by 4 different readers.

Secondary Objectives:

- To test whether the AliveCor device will be non-inferior to the 12 lead ECG with respect to diagnosis of the arrhythmia when read by a Consultant Electrophysiologist.
- To compare the screening characteristics of the AliveCor's automated diagnostic algorithm with its screening characteristics when read by a Consultant Electrophysiologist, a general Consultant Cardiologist and a General Practitioner.

3 Study Design

3.1.1 General

Open label non-randomised diagnostic study. Readers will be blinded to the ECG diagnosis.

Expected study duration: 2 years

3.1.2 Study procedure

Every patient will be counselled about the project by a member of the Cardiology / Cardiology research team (doctor or qualified research nurse) and will be provided with a patient information sheet. Patients will be given up to 2 weeks to consider participation in the study. If in agreement, written informed consent will be obtained.

A 30-second ECG tracing will be obtained by simply holding the Smartphone and placing at least 1 finger from each hand on electrodes embedded into the back of the Smartphone case (figure 2). For sedated patients in the cath lab, AliveCor electrodes will be placed and taped on patient chest wall, left parasternal third intercostal space. A 12-lead ECG will also be recorded as near to simultaneously as possible. The 12-lead ECG will be reviewed by Principal Investigator (PI) to ensure that the ECG rhythm has not changed.

3.2 Primary Study Endpoints

Sensitivity and screening characteristics of AliveCor recording to detect cardiac arrhythmias.

3.3 Secondary Study Endpoints

To test whether AliveCor is non-inferior to the 12-lead ECG.

To compare the screening characteristics of the automated AliveCor algorithm to that of a Consultant Electrophysiologist, general Consultant Cardiologist and General Practitioner.

3.4 End of study

The study will end on the date the last patient completing the protocol.

4 Methods

4.1 Participant Selection and Withdrawal

Patients can be recruited from different cardiology clinics; at the end of an exercise test to record sinus tachycardia, and in the catheter lab during electrophysiological studies/ ablation procedures to record arrhythmias. Participants can withdraw from the study at any time and their standard care pathway will not be affected. If a participant decided to withdraw from the study at any point, we will continue to use any data collected up to withdrawal date.

4.1.1 Inclusion Criteria

1	Male or female patients
2	Age > 18
3	12 lead ECG finding of sinus rhythm, arrhythmia and manifest pre-excitation

4.1.2 Exclusion Criteria

1	Patients <18 years of age.
2	Patients unable to or unwilling to use the device.
3	Patients with cardiac pacemaker, ICDs, or other implanted electronic devices

4.2 Participant Recruitment and Screening

Patients with known positive ECG findings can be recruited from different cardiology clinics, following exercise testing, and in the catheter lab during electrophysiological study/ ablation.

Every patient will be counselled about the project by a member of cardiology / research team (doctor or qualified research nurse) and will be provided by a patient information sheet. Patient will be given choice to take up to 2 weeks to consider participation in the study. If in agreement, written informed consent will be obtained.

4.3 Randomisation Process

This is a diagnostic comparative study. No randomisation is required.

4.4 Informed Consent

Every patient will be counselled about the project by a member of cardiology / research team (doctor or qualified research nurse) and will be provided with a patient information sheet. Patients will be given up to 2 weeks to consider participation in the study. If in agreement, written informed consent will be obtained.
A copy of the consent form is included as an appendix.

4.5 Withdrawal of Participants

Participants can withdraw from the study at any time. This study is a diagnostic study and does not involve follow up visit.

5 Study Procedures

- List of patients details (name and DOB) with study number will be kept safely in a locked cupboard in research office, cardiac education centre, Blackpool Victoria Hospital. This can only be accessed by Principal Investigator and research team members.
- Each patient will be given ID 'for example AC-001'. For 12 lead ECG 'AC-ECG-001' and for AliveCor recording 'AC-AliveCor-001'.
- A 30-second ECG tracing will be obtained by simply holding the Smartphone and placing at least 1 finger from each hand on electrodes embedded into the back of the Smartphone case (figure 2). For sedated patients in the catheter lab, AliveCor electrodes will be placed and taped on patient chest wall, left parasternal third intercostal space. The AliveCor ECG tracing will be recorded as close to simultaneously as the 12 lead ECG recording as possible.
- All 12 lead ECGs will be anonymised and kept safely in locked cupboard in research office, cardiac education centre, Blackpool Victoria Hospital. This can only be accessed by Principal Investigator and research team members.

- All data will be stored anonymously on the Trust Server in a folder called 'AliveCor Study'. This will be password protected. Only PI will have access to this folder.

- All AliveCor traces (anonymised) will be sent electronically via secure trust enabled device to the PI who will store these traces on folder 'AliveCor Study' as described above.

Figure 2

6 Statistical Plan

Statisticians within the Sponsor organisation wrote and designed the sample size calculation and statistical description method.

6.1 Sample Size Determination

With a sample size of 50 patients with one arrhythmia, a sensitivity of 80% would produce a 95% confidence interval of 68.9% to 91.1%. With a sample size of 250 (all arrhythmias combined), a sensitivity of 70% would produce a 95% confidence interval of 64.5% to 75.1%, i.e. an absolute error of ± 5%.

The main secondary end-point will be to compare the sensitivity of a Consultant Electrophysiologist in detecting all arrhythmias using the AliveCor device *vs* the originally coded 12-lead ECG, to test whether the AliveCor device is non-inferior to the original 12-lead ECG diagnosis. Assuming a 95% one-sided confidence interval and a power of 80%, if there is a true difference in sensitivity in favour of the 12-lead ECG over an AliveCor ECG of 10%, and then a sample size of 301 arrhythmias would be needed to exclude a difference in favour of the 12-lead ECG of more than 16%.

6.2 Statistical Methods

The diagnostic sensitivity, screening characteristics and accuracy of the AliveCor device will be reported for each arrhythmia individually and for all arrhythmias combined, measuring 95% confidence intervals using the binomial exact method.

Non-inferiority will be assessed for each arrhythmia individually, and all arrhythmias combined for a Consultant Electrophysiologist reading the AliveCor generated ECG *vs* a near-simultaneously recorded 12-lead ECG.

The Chi-squared test and Fisher's exact test will be used to compare proportions. The McNemar test will be used to compare paired dichotomous dependent variables.

6.3 Interim Analyses

No interim follow-up is planned as this is a diagnostic study. There is no therapeutic intervention in this study. However, the Principal Investigator will be closely monitoring this study and its progression.

7 Safety and Adverse Events

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no Manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA)

database: Manufacturer and User Device Facility Experience (MAUDE).[10] No drug or intervention in this study. All Adverse Events (AE) will be recorded according to the R&D Office Procedure and the Trust Policy on Incident Reporting.

7.1 Recording of Adverse Events

All Adverse Events (AE) Serious Adverse Events (SAE) will be recorded according to the R&D Office Procedure and the Trust Policy on Incident Reporting.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Data Protection Act and the UK Policy Framework for Health and Social Care Research

The identifiable details (Hospital number and date of birth) will be collected from participants in this study.

Principal Investigator will have access to this information

Data will be anonymised if placed on a computer database. Patient will be given a study ID (AliveCor 001, AliveCor 002, etc.) as per order of recruitment.

The Principal Investigator is the custodian of the data.

8.2 Case Report Forms

The study case report form (CRF) is the primary data collection instrument.

- All data requested on the CRF/DCF will be recorded.
- All missing data must be explained. If a space on the CRF/DCF is left blank because the procedure was not done, or the question was not asked, we will write “N/D”.
- If the item is not applicable to the individual case, we will write “N/A”.
- All entries should be printed legibly in black ink.
- To correct any data entry error, will draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated.

8.3 Records Retention

Period of record retention will be 5 years

Filing arrangements for the CRFs and consent forms will be kept in research office in Lancashire Cardiac Centre, Blackpool Victoria Hospital. Records will also be archived in line with R&D Standard Operating Procedures (SOP).

9 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, audits and inspections by the Ethics Committee, the Sponsor and the Research Governance Manager.

Participation as an investigator in this study implies adherence to the principles and responsibilities of the UK Policy Framework for Health and Social Care Research, ICH/GCP and Directive 2000/20/EC.

10 Ethical Considerations

Informed consent will be obtained from each participant as detailed in the consent section.
Data protection will be ensured throughout the study. The data will be anonymous and information governance guidelines will be religiously followed to ensure confidentiality.
No added potential harm could be caused to any participant from the use of the AliveCor device.
The study will not be funded by any company with an interest into their desired outcome.
Investigators participating in the study must declare no conflict of interest.

This study will be conducted according to the standards of International Conference on Harmonization, Good Clinical Practice Guideline, Health Research Authority regulations, any applicable government regulations, Trust and Research Office policies and procedures.

This protocol and any amendments will be submitted to the Health Research Authority for review and approval of the study conduct.

No research studies can commence until the principal investigator has received a letter Confirming Capability and Capacity from the Trust issued by the Research and Development Office and a letter of approval from the Health Research Authority and REC.

10.1 Patient information Sheets

All participants for this study will be provided with an information sheet describing the elements of this study and sufficient information for subjects to make an informed decision about their participation in this study.

11 Indemnity

NHS indemnity will apply.

12 Sponsorship:

This study is a single-centre study as is sponsored by Blackpool Teaching Hospitals NHS Foundation Trust, the PI‘s employer.

13 Publication Plan

Principal Investigator will be responsible to publish these data in a peer-reviewed journal.

14 References

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