Trial Title	**Randomised controlled trial of the use of a smart phone based event recorded versus standard care for patients presenting to the Emergency Department with palpitations and pre-syncope (The IPED study)**
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List of abbreviations

AE	Adverse Event
AMU	Acute Medical Unit (or equivalent)
BP	Blood Pressure
CHB	Complete Heart Block
CI	Chief investigator
CRF	Case Report Form
ECG	Electrocardiogram
ED	Emergency Department
EPS	Electrophysiology study
GP	General Practitioner
ICD	Implantable Cardioverter Defibrillator
IPED	Investigation of Palpitations in the ED
IQ	Interquartile
MACE	Major Adverse Cardiac Event
NHS	National Health Service
SAE	Serious Adverse Event

1. *Introduction*

The following document contains a description of the planned analysis for the IPED study. The full description of the study is available from the study protocol. However, in brief, this study aims to determine if using a smart phone event recorder will allow Emergency Department (ED) patients who have presented with palpitations or pre-syncope to record their Electrocardiogram (ECG) tracing if they have a further episode increasing the rate of underlying rhythm diagnosis.

2. *Study design*

This is a multi-centre hospital ED/Acute Medical Unit (AMU) open label, randomised controlled trial of participants aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythm during these episodes remains undiagnosed after ED assessment. Participants will be followed-up at 90 days using hospital records, contacting participant General Practitioner (GP) and also by contacting the participants themselves. This study is expected to take around 18 months to complete from first participant recruited to last participants' 90-day follow-up.

2.1. Number of participants

242 consecutive participants aged 16 years or over presenting with an episode of palpitations or pre-syncope and whose underlying ECG rhythm during these episodes remains undiagnosed after ED assessment shall be recruited into the study. Recruitment will last around 15 months.

2.2. Study endpoints

The primary endpoint is the symptomatic rhythm detection rate of a smart phone based event recorder (AliveCor Monitor) for symptomatic rhythm detection at 90 days versus standard care for participants presenting to the ED with palpitations and pre-syncope with no obvious cause in the ED.

The secondary endpoints are:

1. Symptomatic rhythm detection rate of a smart phone based event recorder for cardiac arrhythmia detection at 90 days versus standard care.
2. Time to detection of symptomatic rhythm using a smart phone based event recorder versus standard care.
3. Time to detection of cardiac arrhythmia rhythm using a smart phone based event recorder versus standard care.
4. Number of participants treated or (planned for treatment) for cardiac arrhythmia in participants using a smart phone based event recorder versus standard care.

5. Participant satisfaction and monitor compliance.
6. Cost effectiveness analysis.
7. Serious outcomes at 90 days: all cause death and major adverse cardiac events (myocardial infarction, life-threatening arrhythmia, insertion of a pacemaker or internal cardiac defibrillator, insertion of pacing wire).

2.3. Adverse events

A secondary endpoint for the study is serious outcomes at 90 days: all cause death and major adverse cardiac events [MACE] (myocardial infarction, life-threatening arrhythmia, insertion of a pacemaker or internal cardiac defibrillator, insertion of pacing wire). This data will therefore be routinely collected as part of the study and not recorded as an Adverse Event (AE). Hospital admission will also not be recorded as an AE. The only AEs recorded will be those directly related to the use of the smart phone based event recorder and application.

3. Statistical methods from protocol

Descriptive analysis of participant characteristics shall be presented split by study arm. Baseline to 90 day change in diagnostic yield between the two study arms will be analysed using two sample t-tests or non-parametric equivalent as appropriate. Log-rank tests and Kaplan-Meier curves shall be used to examine if the smartphone recorder has an effect on detecting symptomatic rhythm and cardiac arrhythmia separately up to 90 days versus standard care. Categorical variables will be compared using a $\chi 2$ test (and $\chi 2$ test for trend if appropriate). All participants will be analysed on an intention to treat basis.

4. Study methods

4.1. Randomisation and treatment allocation

Participants will be equally distributed between the two study arms. Randomisation will be by block randomisation by site. An equal number of sealed opaque envelopes containing either 'Standard Care plus Device' or 'Standard Care' cards will be prepared by a central administrator not involved in the study. These will then be randomly labelled with site-specific study participation numbers and sent to each local study team. Participants eligible for inclusion will be randomised by the local study team by taking the next lowest consecutively numbered sealed opaque envelope. There will be no stratification or minimization factors.

Participants will be allocated either to (a) STUDY arm; standard care plus the use of a smart phone based event recorder or (b) CONTROL arm; standard care, depending on the group allocated in the study envelope.

4.2. Study assessments

4.2.1. Screening and baseline assessments

Potentially eligible participants will be identified and assessed for study inclusion by the attending clinician. Written consent will be taken and participants will have a Case Report Form (CRF) completed and a 12-lead ECG taken if not already performed by the clinical team.

Participants in both groups will be admitted, referred or discharged by the treating clinician according to current local hospital protocols.

4.2.2. Follow up assessments

Participants in both groups will be followed up at 90 days through hospital record systems (paper or electronic depending on local policy), GP records and by telephone by the local study team. Participants will also be asked to complete a standardised written questionnaire and will receive a follow-up telephone call from the local study team enquiring about symptoms and contact with medical services. Study arm participants will also be asked about satisfaction and compliance with the heart monitor.

Participants allocated to the Study arm may be contacted by telephone by the local research team shortly after randomisation in the event of them requiring further training or setting up of the device.

If a participant allocated to the Study arm gets an episode of palpitations or pre-syncope and is able to record an AliveCor Heart Monitor ECG during the episode, the participant will email the ECG recorded by the AliveCor app directly to the co-ordinating Edinburgh research team at a convenient time to the participant and to a secure nhs.net email address.

The co-ordinating Edinburgh research team will review the ECG and will contact the local study team to arrange follow-up if required. If specialist follow-up of the ECG tracing is not required then the local study team will write to the participant informing them of this and ask them to arrange follow up with their general practitioner who will be contacted with the report. The participant and GP will not be contacted further should participants record other similar ECGs that similarly do not require specialist follow-up.

If the participant records a serious significant arrhythmia during the study period, the local study team will alert the participant immediately by telephone, and refer them urgently to their local Emergency Department or cardiac electrophysiology service (as per local protocol).

4.2.3. Participant symptom diary, satisfaction and compliance

Participants will be asked to log any symptoms along with the time and date, type of symptom and whether they were able to record an ECG during the symptoms, in a participant symptom diary. They will return this diary to the local research team along with the participant satisfaction and compliance questionnaire, and smart phone based event recorder at the end of the 90 days. Participants will be phoned at 90 days by the local study team to remind them to complete the participant satisfaction and compliance questionnaire and to return this to the local study team with the symptom diary and smart phone based event recorder. The compliance questionnaire is designed to capture whether participants had the device with them and were able to record a heart tracing during symptoms. Detail the specific study assessments to be performed and the time points during the study - split by visit number if appropriate for clarity. It may be appropriate to prepare a table of assessments by visit.

5. General Considerations

5.1. Overall

For all analyses, unless otherwise specified, participants shall be analysed according to treatment received, irrespective of the treatment group they were allocated to, with the exception of AE/SAEs. An additional table will be provided on whether the participant took part in the study and if they did not then their AE/SAEs will be includes as part of the control group.

5.1.1. Timing of final analysis

The final analysis will be performed after the required number of patients has been recruited and will be performed on the data set after any 'cleaning' that may be required has been completed and the database locked. There are no plans to perform an interim analysis.

5.1.2. Missing data

No imputation for missing data shall be performed. The primary outcome analysis will only be performed on those participants with 90 day follow up, however a table to data completeness shall be provided which will capture any participants who were lost to follow-up.

6. *Final analysis*

6.1. Recruitment and data completeness

Standard accrual plot and plot of number of participants recruited each quarter. Recruitment date shall be date of consent into the study.

A table presenting the completeness of participant data shall also be provided.

6.2. Baseline demographic statistics

The following participant details shall be presented split by allocated study arm. Where data are continuous the mean, standard deviation, median, interquartile (IQ) range and range shall be presented and where data are binary or categorical the frequency and percentage shall be presented:

- Participant demographics
- History of presenting episode
- Past medical history
- Examination
- Admission ECG
- Management

6.3. Primary outcome

The baseline to 90 day change in diagnostic yield (i.e. presence/absence symptomatic rhythm detection) of a smart phone based event recorder compared with standard care only shall be analysed using a comparison of proportions test.

6.4. Secondary outcomes

1. The baseline to 90 day change in cardiac arrhythmia detection (i.e. presence/absence) of a smart phone based event recorder compared with standard care only shall be analysed using comparison of proportions test.
2. A log-rank test and Kaplan-Meier curves shall be used to examine if the smartphone recorder has an effect on time to first detection of symptomatic rhythm up to 90 days versus standard care only.
3. A log-rank test and Kaplan-Meier curves shall be used to examine if the smartphone recorder has an effect on time to first detection of cardiac arrhythmia rhythm up to 90 days versus standard care only.

4. The number of participants treated (or planned for treatment) for cardiac arrhythmia in those using a smart phone based event recorder versus standard care only shall be analysed using a comparison of proportions test.

5. Participant satisfaction questionnaire responses shall be compared between study arms using χ^2 test(s) (and χ^2 test(s) for trend if appropriate). A similar analysis shall be performed for participant compliance questionnaire responses.

6. The number of participants recorded for each of the following shall be collated. If appropriate and numbers allow, a two-sample t-test (or non-parametric equivalent as appropriate) shall be used to compare study arms where the outcome of interest is continuous. However if the numbers are to be treated as categorical then a χ^2test (and if appropriate, χ^2 test for trend) shall be used to compare study arms:

   - Number of ED presentations (except index visit) due to palpitations/pre-syncope.
   - Number of inpatient hospital days (over all admissions) due to palpitations/pre-syncope.
   - Number of outpatient presentations due to palpitations/pre-syncope.
   - Number of GP presentations due to palpitations/pre-syncope (via phone follow-up).
   - Number of TRAK ECGs due to palpitations/pre-syncope.

   A comparison of the overall cost-effectiveness of the smart phone based event recorder and standard care shall be provided using a two-sample t-test (or non-parametric equivalent as appropriate) between study arms. The costing scope will include primary care, secondary care and community NHS costs which shall be provided separately by the CI for analysis.

7. The number of participants recording at least one serious outcome at 90 days in those using a smart phone based event recorder compared to standard care only shall be examined by a comparison of proportions test. Following on from this the number of serious outcomes at 90 days between the two study arms shall be examined using a χ^2 test (and χ^2 test for trend if appropriate).

6.5. Post-hoc analysis – participants with positive symptomatic rhythm only

Considering only those participants where a positive symptom rhythm was identified, the following section will details univariate and potential multivariate logistic regression analysis using type of arrhythmia as the outcome variables of interest (cardiac arrhythmia vs. all other arrhythmia).

6.5.1. Univariate logistic regression

The pre-defined baseline/presentation variables of interest are as follows:

- Gender (*male/female*).
- Age *(years*).
- Number of episodes in last 24 hours.
- Estimated length of presenting episode (*1 minute or less/10 minutes or less/1 hour or less/More than 1 hour*).
- Patients' description of symptoms (*each symptom to be analysed individually as 'Yes'/'No; Unknown'*).
- How often do they occur? (*Never had before/Yearly/Monthly/Weekly/More than once a week*).
- How do the palpitations start? (*Suddenly/Gradually*).
- Can the palpitations be provoked? (*Yes/No*).
- How do the palpitations end? (*Suddenly/Gradually*).
- Can the patient end the attacks? (*Yes/No*).
- Recent alcohol (4 units or more in last 24 hours)? (*Yes/No*).
- Recent (last 7 days) febrile illness? (*Yes/No*).
- Previous/known hypertension/ischemic/coronary/valvular heart disease/failure? (*Yes/No*).
- Initial Pulse at triage.
- Initial Systolic BP at triage.
- QRS axis.
- QTc int.
- PR >200 mseconds (*Yes/No).*
- Slow rise in the initial portion of the QRS? (*Yes/No).*
- Heart block? (*Yes/No).*

- QRS duration ≥ 120 mseconds? (*Yes/No)*.
- Number of ventricular ectopics?
- Proportion of diary records out of the 'Number of records in symptom log' rated as: Anxious, Arm or neck pain/tingling, Chest pain or pressure, Dizziness, Fainted, Light headed, Pounding, Fluttering or racing, Short of breath, Skipped /missed beat(s), Irregular beating.
- Number of diary records rated as: 1 minute or less, 10 minutes or less, 1 hour or less, More than 1 hour.

6.5.2. Multivariate logistic regression

The following analysis will only be conducted if the number of events observed (cardiac arrhythmias and other arrhythmias) during the study period is sufficient.

A multivariate logistic regression model shall be examined to see if including any of the variables from the univariate analysis (chosen by the CI and with $p<0.1$) can produce a model which helps to predict a participants' risk of cardiac arrhythmia. The model's stability shall be verified using both forward and backward stepwise procedures.

7. Revision History

Document version & date	Review comment	Date of review	Reviewer's Signature