



Randomised controlled trial of the use of a smart phone based event recorder versus standard care for patients presenting to the Emergency Department with palpitations and pre-syncope

The IPED (Investigation of Palpitations in the ED) study

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## Study Protocol

Randomised controlled trial of the use of a smart phone based event recorder versus standard care for patients presenting to the Emergency Department with palpitations and pre-syncope

### The IPED study

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## PROTOCOL APPROVAL

The IPED study

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Chief Investigator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

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Study Statistician

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

Susan Shepherd  
Sponsor(s) Representative

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AF	Atrial Fibrillation
AMU	Acute Medical Unit (or equivalent)
AR	Adverse Reaction
CHSS	Chest, Heart & Stroke, Scotland
CRF	Case Report Form
CV	Curriculum Vitae
GCP	Good Clinical Practice
ECG	Electrocardiogram
ED	Emergency Department
EMERGE	Emergency Medicine Research Group of Edinburgh
EPR	Electronic Patient Record
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MACE	Major Adverse Cardiac Event
NYHA	New York Heart Association
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVT	Supraventricular Tachycardia
TMF	Trial Master File
UAR	Unexpected Adverse Reaction
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

## **SUMMARY**

Palpitations (noticeable pounding, fluttering or irregular heart beat) and pre-syncope (near blackout) are common ED problems sometimes due to an abnormal cardiac rhythm. This is difficult to diagnose as examination and electrocardiogram (ECG) are commonly normal and symptoms have usually resolved by the time the patient arrives in the ED. Diagnosing an abnormal heart rhythm as the cause of symptoms rests on capturing it on an ECG and patients are usually discharged with advice to return to the ED again for a 12-lead ECG should symptoms recur. We believe a smart phone based event recorder will allow better and earlier diagnosis in patients with a compatible smart phone or tablet, and revolutionise ED care in this area.



# 1 INTRODUCTION

## 1.1 BACKGROUND

Palpitations (the noticeable pounding, fluttering or irregular beating of the heart) and pre-syncope (the sudden onset of a sense of impending loss of consciousness) are together responsible for 1.0% of ED visits (300,000 annual ED attendances in the UK) [1,2]. They are less likely to be due to serious arrhythmia than syncope (sudden onset of brief loss of consciousness) and are more likely due to conditions such as atrial fibrillation (AF) and supraventricular tachycardia (SVT). Diagnosis of the underlying rhythm is difficult as many patients are fully recovered on ED arrival and examination and presenting ECG are commonly normal. Many episodes are due to benign causes such as anxiety or frequent ectopics (extra or skipped heart beats).

The only way to establish the underlying heart rhythm is to capture an ECG during symptoms. Many patients go for years without diagnosis due to the difficulty in capturing the underlying heart rhythm. 12-lead ECG and conventional ambulatory devices are of limited use due to the infrequency of symptoms in many patients. Most are discharged from the ED and asked to represent or phone 999 should they get further symptoms in the hope of capturing the episode on a standard 12-lead ECG.

Recent technology advances have led to several novel ECG monitoring devices appearing on the market. The Emergency Medicine Research Group, Edinburgh (EMERGE) with CHSS support, is currently evaluating a continuous ambulatory ECG monitor (ZIO@XT Patch) for use in syncope patients. This is a pilot study aiming to recruit 100 participants by December 2016. Devices that continuously monitor are vital to detect underlying cardiac rhythm in patients with syncope as the patient has lost consciousness and is therefore not able to use devices that require the patient to trigger the ECG recording (event recorders).

The pocket sized AliveCor Heart Monitor and AliveECG phone/tablet app is a monitoring device that requires the patient to trigger the ECG recording. It is available for both Apple and Android mobile and tablet operating systems and was CE marked in January 2015 [3]. With minimal training, two fingers from each hand are placed on the monitor (which can be connected to the back of a smart phone) for 30 seconds to take an ECG recording, which is transmitted wirelessly to the app, analysed and synchronised to an encrypted server. The patient can then alert their healthcare professional to allow their ECG to be viewed securely [3].

The Arrhythmia Alliance [3] distributed AliveCor Heart Monitors to 1500 people of all ages. Only one returned their monitor because it caused them to worry and check their heart rate too often. 26% of recordings showed a previously undetected arrhythmia and 5% were advised to see their doctor urgently. They reported the AliveCor Monitor was 'easy for people of all ages to use, and could save money for the NHS when compared with the cost of standard NHS ECG recordings.' Older people were also noted to be regular users of mobile technology and gave positive feedback about the system.

## 1.2 RATIONALE FOR STUDY

There have been few studies investigating the use of smart phone based event recorders [4-7], and none in an acute or ED population, where large numbers of patients present. We believe this smart phone event recorder will allow ED patients who have presented with palpitations or pre-syncope to record their ECG tracing if they have a further episode increasing the rate of underlying rhythm diagnosis.

## **2 STUDY OBJECTIVES**

### **2.1 OBJECTIVES**

#### **2.1.1 Primary Objective**

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

#### **2.1.2 Secondary Objectives**

1. To investigate the symptomatic rhythm detection rate for cardiac arrhythmia detection at 90 days of a smart phone based event recorder compared to standard care for participants presenting to the ED with palpitations and pre-syncope
2. To compare the time to detection of symptomatic rhythm versus standard care
3. To compare the time to detection of cardiac arrhythmia versus standard care
4. To compare the number of participants treated or (planned for treatment) for cardiac arrhythmia versus standard care
5. To investigate participant satisfaction and monitor compliance
6. To compare the cost of symptomatic rhythm detection at 90 days of a smart phone based event recorder compared to standard care for participants presenting to the ED with palpitations and pre-syncope
7. To compare serious outcomes at 90 days in participants using a smart phone based event recorder compared to standard care

#### **2.1.3 Primary Endpoint**

Symptomatic rhythm detection rate of a smart phone based event recorder for symptomatic rhythm detection at 90 days versus standard care.

#### **2.1.4 Secondary Endpoints**

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 [MACE] (myocardial infarction, life-threatening arrhythmia, insertion of a pacemaker or internal cardiac defibrillator, insertion of pacing wire).

## **3 STUDY DESIGN**

This is a multi-centre hospital ED / 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 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.

## **4 STUDY POPULATION**

### **4.1 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.

### **4.2 INCLUSION CRITERIA**

1. Participant aged 16 years or over
2. Participant presenting with an episode of palpitations or pre-syncope with no obvious cause
3. Participant's underlying ECG rhythm during these episodes remains undiagnosed after clinical assessment.

### **4.3 EXCLUSION CRITERIA**

1. Prior diagnostic ECG
2. Palpitations or pre-syncope present during an admission ECG
3. Frequent episodes (i.e. at least once a day)
4. Participants under 16 years of age
5. Previous participation in the study
6. Alcohol / illicit drugs / seizure / stroke / transient ischemic attack / head trauma / hypoglycemia as presumptive cause
7. Inability or unwilling to give informed consent.
8. Participants with recent (i.e. within 3 months) myocardial infarction, severe heart failure (NYHA class 4) or unstable angina
9. Participants unwilling or unable to use the AliveCor Heart Monitor and AliveECG app
10. Participants without a compatible smart phone or tablet
11. Participants with cardiac pacemakers or other implanted electronic devices
12. No telephone number for follow-up
13. Participant in custody

### **4.4 CO-ENROLMENT**

Co-enrolment will be permitted with non-interventional studies that involve data collection only. Co-enrolment with another interventional study may be allowed provided this is not expected to place an undue burden upon participants and their families, and will not compromise the primary end-point of either study. Consideration will also be given to the burden on the participant. Co-enrolment will only be permitted with agreement of the Chief Investigators of both studies.

## **5 PARTICIPANT SELECTION AND ENROLMENT**

### **5.1 IDENTIFYING PARTICIPANTS**

The research nurses, where it is locally agreed that they are part of the clinical care team, will identify patients using triage information and clinical or electronic records in the ED or the AMU. In this case, it is anticipated they would identify patients and make the first approach. Any member of the clinical team who has received general and trial specific training and is on the delegation log may also identify patients in this way.

If research nurses are not considered to be part of the direct care team locally, activities carried out prior to consent (including identification) will be carried out by a member of the direct care team.

Where research nurses are not considered to be part of the care team, the research nurse should ask a member of the direct care team to identify suitable patients and ask permission from the patient to be approached by the research nurse to discuss participation.

## **5.2 CONSENTING PARTICIPANTS**

If the potentially eligible participant fulfils the study eligibility criteria, a member of the study research team (or direct care clinician if suitably trained) will take written consent.

The participant is assessed by the direct care team to establish if he/she is competent and has capacity to consent. This assessment will be documented in the medical notes i.e. this participant is eligible and capable of providing written informed consent. Participants lacking capacity who are unable to provide consent will not be approached to take part in the study.

The participant (and, if present and appropriate, their accompanying relative) will be given a Participant Information Sheet, which will explain the aims of the study and the potential risks and benefits of the study procedures/tests.

The participant will be given enough time to consider the study and ask questions regarding their participation in the study. For some participants this could be as much as an hour but for others may only be 10-15 minutes. If the participant agrees, informed consent will be confirmed with a signature on the study consent form. The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy will be filed in the participant's medical notes.

Potential, eligible participants who are able to express their consent and able to complete the consent form will be asked to provide written consent. The recruiting direct care clinician or member of the research team will do this. A witness will sign to confirm that all the study information was given and the participant consented to taking part in the study for participants who are able to express their consent but unable to sign.

## **5.3 SCREENING FOR ELIGIBILITY**

There is a requirement to ensure Good Clinical Practice for published studies and to include a Consort diagram [8] of numbers of participants with the study condition during the study period who for one reason or another were not enrolled in the study. In order to determine the number of eligible but not recruited participants during the study period, the ED patient record of all potentially eligible participants will be interrogated by a member of the study research team (if part of the participant's direct care team).

An anonymised log will be kept for patients who were screened for the study and those who were subsequently found to be ineligible or who were not recruited.

## **5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS**

Non-recruited but potentially eligible participants will be identified by a daily search of all acute patient admissions records to assess for potential selection/recruitment bias. Ineligible patients will not be recorded.

## **5.5 RANDOMISATION**

### **5.5.1 Randomisation Procedures**

Participants will be equally distributed between the two study arms with 121 participants in each arm. Randomisation will be by block randomisation. Randomisation codes will be generated and blinded envelopes will be prepared and labelled in accordance with the randomisation list for each participating site. Randomisation codes will be held by each recruiting ED in an area of the ED accessible to the research team. Participants eligible for inclusion should be randomised by taking the next lowest consecutively numbered envelope.

### **5.5.2 Treatment Allocation**

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.

### **5.5.3 Withdrawal of Study Participants**

If a participant wishes to withdraw from the study they will be removed. We will establish whether they consent to allow the use of all data collected up to the date of removal. They will not be replaced.

## **6 STUDY ASSESSMENTS**

### **6.1 SAFETY ASSESSMENTS**

This study has been risk assessed by the Medical Physics and Infection Control teams at the Royal Infirmary of Edinburgh. An Infection Control agreed SOP for cleaning the AliveCor Heart Monitor Device prior to re-use is included in the study paperwork.

### **6.2 STUDY ASSESSMENTS**

Potentially eligible ED and AMU 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.

All STUDY arm participants will be given an AliveCor Heart Monitor and trained in the use of the device and app in the ED or AMU by the research team.

CONTROL arm participants will receive no other intervention.

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

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. 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. For example, this may be necessary if a participant does not have their app store password with them in the ED or AMU. If a local electronic patient record system is available, then a research alert will be placed on this stating that the participant has consented to be part of the IPED study.

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. This email includes a pdf attachment of the ECG tracing along with the participant's AliveCor app login (which will be their IPED study number - no identifiable participant data will leave the local site, only the participants email address and IPED study number will appear), time and date of recording, and ECG recording. AliveCor collects non-sensitive usage data through a third party service called Mixpanel. Participant will not be asked to send their ECGs to AliveCor directly for analysis. The AliveCor app rhythm analysis algorithm will automatically report any ECG recorded by the AliveCor app as Normal, Atrial Fibrillation or Unclassified.

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 (Patient ECG follow-up letter normal v2.0 24082016 and Patient ECG follow-up letter abnormal v2.0 24082016) and asking them to arrange follow up with their general practitioner who will be contacted with the report (GP Follow up Letter v2.0 24082016). 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 i.e.

- ventricular fibrillation (VF)
- ventricular tachycardia (VT) (it will be assumed that this is symptomatic given the participant has chosen to record an ECG during the episode)
- complete or 3rd degree heart block
- second degree heart block type II (it will be assumed that this is symptomatic given the participant has chosen to record an ECG during the episode)
- pause >6 seconds
- symptomatic bradycardia <40 beats per minute

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).

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 in a pre-paid stamped, addressed envelope. 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. This will be entered onto the study database by the local study team.

## **7 DATA COLLECTION**

Participants will have a CRF completed during index hospitalisation, comprising demographic, historical and examination characteristics. An ECG will also be taken and stored. Participant contact details will also be confirmed including a telephone number and email address. Once a participant has been randomised, the baseline CRF will be sent to the local study team office. The information on the CRF will be entered into a specially designed password protected online accessed secure database (REDCAP; <http://www.project-redcap.org>) the server of which is held within the University of Edinburgh. No participant identifiable information will leave the recruiting NHS hospital or be entered onto REDCAP. Participants will be identified on REDCAP by study number alone.

## **8 STATISTICS AND DATA ANALYSIS**

### **8.1 SAMPLE SIZE CALCULATION**

Using a symptomatic rhythm detection rate at 90 days of 25% [3] versus standard care (10%) we estimate 110 participants in each group would have 80% power to determine a 15% improvement in symptomatic rhythm detection. We will recruit an extra 10% in each arm to allow for drop out (i.e. 121 participants in each arm). Our ED sees around 500 eligible participants a year. Assuming a 50% recruitment rate we estimate we will need to recruit for 15 months.

### **8.2 PROPOSED ANALYSES**

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.

## **9 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.

## **10 PREGNANCY**

Pregnancy is not an exclusion criteria for the IPED study.

## **11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS**

### **11.1 TRIAL MANAGEMENT GROUP**

The study will be coordinated by a Project Management Group consisting of the Chief Investigator, Co-Investigators, Statistician and Research Team.

EMERGE will oversee the study and will be accountable to the Chief Investigator. EMERGE will be responsible for checking the electronic CRFs for completeness, plausibility and consistency. The Chief Investigator and EMERGE will resolve any queries.

A Delegation Log will be prepared detailing the responsibilities of each member of staff working on the study.

### **11.2 TRIAL STEERING COMMITTEE**

A Trial Steering Committee (TSC) has not been convened for this study. An independent advisor has been appointed to oversee the conduct and progress of the study.

### **11.3 DATA MONITORING COMMITTEE**

An independent Data Monitoring Committee (DMC) has not been convened for this study.

### **11.4 INSPECTION OF RECORDS**

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the sponsor, Research Ethics Committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring process being implemented, the Investigators agree to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the CI agrees to allow inspectors direct access to all study records and source documentation.

### **11.5 RISK ASSESSMENT**

An independent risk assessment may be performed by an Academic and Clinical Central Office for Research and Development (ACCORD) Clinical Trials Monitor to determine if monitoring is required and if so, at what level although this is unlikely as the study is not a CTIMP or high risk study. An independent risk assessment may also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

### **11.6 STUDY MONITORING AND AUDIT**

An ACCORD Clinical Trials Monitor or an appointed monitor may visit the Investigator's site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of the Investigator's site,

study management activities and study collaborative units, facilities and 3<sup>rd</sup> parties may be performed.

## **12 GOOD CLINICAL PRACTICE**

### **12.1 ETHICAL CONDUCT**

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP) and the Research Governance Framework for Health and Community Care (Scotland) 2006 [9].

A favorable ethical opinion will be obtained from the appropriate REC and local Research and development (R&D) approval will be obtained prior to commencement of the study.

### **12.2 INVESTIGATOR RESPONSIBILITIES**

The Principal Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

#### **12.2.1 Informed Consent**

The Principal Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Principal Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Principal Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

#### **12.2.2 Study Site Staff**

The Principal Investigator must be familiar with the protocol and the study requirements. It is the Principal Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

#### **12.2.3 Data Recording**

The Principal Investigator is responsible for the quality of the data recorded in the CRF at the Investigator Site.

#### **12.2.4 GCP Training**

The Chief Investigator, Principal Investigators and Lead Research Nurse Co-ordinator should hold evidence of GCP training and ensure staff are aware of the guidelines. All staff on the delegation log should have appropriate and relevant training in the research tasks that they undertake.



### **12.2.5 Confidentiality**

All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Principal Investigators and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

### **12.2.6 Data Protection**

Data will be initially collected into a paper CRF and then entered into a specially designed password protected online accessed secure database (REDCAP; <http://www.project-redcap.org>) the server of which is held within the University of Edinburgh. No participant identifiable information will leave the NHS or be entered onto REDCAP. Participants will be identified on REDCAP by study number alone.

Identifiable electronic information will be kept in a separate database, which will not be accessible outside the immediate research team. This data will be linked by study number to the anonymised research database and will be stored on a secure, password protected location on the local hospital computer drive and only accessible to relevant staff.

Identifiable non-electronic data of the participant will be kept in a locked filing cabinet in a locked local research study office.

Data entry will be completed by the local research team and data analysis by the study statistician. No participant identifiable data will be transferred outwith the local NHS region. Participant identifiable data will be removed from electronic data being sent to the University of Edinburgh for analysis.

The Chief Investigator will be responsible for the quality of the data recorded in the electronic CRF on the research database.

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

## **13 STUDY CONDUCT RESPONSIBILITIES**

### **13.1 PROTOCOL AMENDMENTS**

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to participants being enrolled into an amended protocol.

### **13.2 PROTOCOL VIOLATIONS AND DEVIATIONS**

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation.

### **13.3 SERIOUS BREACH REQUIREMENTS**

A serious breach is a breach, which is likely to affect to a significant degree:

- (a) the safety or physical or mental integrity of the participants of the study; or
- (b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the sponsors ([accord.seriousbreach@ed.ac.uk](mailto:accord.seriousbreach@ed.ac.uk)) must be notified within 24 hours. It is the responsibility of the sponsors to assess the impact of the breach on the scientific value of the study, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

### **13.4 STUDY RECORD RETENTION**

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

### **13.5 END OF STUDY**

Clinical interventions expected to finish 31/12/2017. End of the study will be once final analysis has been completed.

The Investigators and sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

### **13.6 INSURANCE AND INDEMNITY**

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the CI and staff. The sponsor, as part of the United Kingdom's Nation Health Service, and will have the benefit of NHS Indemnity.

## **14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

### **14.1 AUTHORSHIP POLICY**

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

### **14.2 PUBLICATION**

The results of our research will be disseminated in the following ways:

1. Summary disseminated to NHS Lothian communication systems including EMERGE intra- and internet sites and all participating sites
2. A media summary
3. Presentation at local and national educational, clinical and research meetings and international research meetings
4. Publication in peer reviewed journals
5. Research report disseminated to NHS Lothian R&D, NHS Research Scotland, and CHSS.

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

### **14.3 PEER REVIEW**

The IPED study received grant funding from CHSS where it underwent peer review and was successfully awarded funding. The patient information sheet, consent form and patient symptom diary and patient satisfaction and compliance questionnaire were reviewed by the EMERGE patient and public involvement group.

## 15 REFERENCES

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