Multi-centre open label randomised controlled trial of immediate enhanced ambulatory ECG monitoring versus standard monitoring in acute unexplained syncope patients: The ASPIRED study.

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v1.0	24.09.2021	Amended during REC review - not implemented
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v3.0	14.03.2022	NSA_14Mar22 minor edits, clarifications and typos corrected
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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AF	Atrial Fibrillation/Flutter
AMU	Acute Medical Unit
AR	Adverse Reaction
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AV	Atrioventricular
BHF	British Heart Foundation
BPM	Beats Per Minute
CI	Chief Investigator
CHI	Community Health Index
CV	Curriculum Vitae
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
ED	Emergency Department
EMERGE	Emergency Medicine Research Group of Edinburgh
EPR	Electronic Patient Record
ESC	European Society of Cardiology
GCP	Good Clinical Practice
GP	General Practitioner
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
ILR	Implantable loop recorder

ISF	Investigator Site File
LQTS	Long QT Syndrome
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
NICE	National Institute of Clinical Excellence
NHS	National Health Service
NYHA	New York Heart Association
PE	Pulmonary Embolus
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QALY	Quality Adjusted Life Year
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SIGN	Scottish Intercollegiate Guidelines Network
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVT	Supraventricular Tachycardia
TLoC	Transient Loss of Consciousness
TMF	Trial Master File
UAR	Unexpected Adverse Reaction
UK	United Kingdom

VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Disease incidence

Syncope (or blackout) is common; 650,000 patients present to UK Emergency Department (ED) every year **[1]**. The 3 underlying causes are vasovagal (simple faint), postural hypotension (blood pressure fall on standing) and cardiac disease (structural heart disease or cardiac dysrhythmia). Diagnosis is difficult and is not apparent in ~50% of patients after assessment **[1]**. Whilst vasovagal and postural syncope are relatively benign, serious pathology (affecting 7 out of every 100 patients at one month after ED attendance **[2]**) include dysrhythmia (an abnormal heart rhythm). When cardiac dysrhythmias are detected, they are most commonly asystolic pauses, reflex bradycardia or advanced atrioventricular block, with tachycardia being the minority **[3].**

The difficulty in the ED is to differentiate between the causes of syncope and identify patients at higher risk. This can be complicated as many patients have fully recovered on ED arrival and their examination and presenting Electrocardiogram (ECG) may both be normal. The lack of efficacy and availability of commonly used monitoring devices means most high and medium risk patients are admitted to hospital for observation and telemetry (if available), with escalating costs. Unfortunately, many (~50% of patients after assessment) still end up being discharged without a diagnosis **[4]**.

In general, syncope reoccurs in around 50% of patients within a year. Recurring episodes impact upon number of hospital admissions, health costs and importantly the quality of life of patients. Whilst there is a wide variation in the literature with respect to the number of syncope episodes and recurrence rates pre and post treatment **[3, 5-7]** once a cardiac dysrhythmia diagnosis is made and treatment initiated, around only 10% of patients will have a 1-year recurrence **[8]** and syncope episodes will drop by over 90% **[8]**. Pacing, the most specific treatment studied shows a syncopal recurrence rate during follow-up of 0–20% versus 20–60% in untreated patients **[3]**.

1.1.2 Current Diagnostic Options

Diagnosis of unexplained syncope remains a challenge in both the ED and cardiology. The current method for establishing cardiac dysrhythmia as the cause of syncope rests on correlating the dysrhythmia with symptoms. Cardiac dysrhythmia investigation is usually initiated with Holter monitoring (a 24 - 48-hour tape) but research has shown non-compliance and lack of extended monitoring reduces diagnostic yield to <20% **[9]**. Event recorders can monitor over longer periods but must be activated. External continuous loop recorders are expensive, bulky, and produce a large amount of data, which requires sifting. Implantable Loop recorders (ILR) are expensive, require a surgical procedure and can result in side effects such as pain and bruising at the implantation site. It is therefore reserved for patients who remain unexplained after thorough initial investigation and is commonly not deployed for months or even years after the index event.

There is evidence that the diagnostic yield for detecting underlying dysrhythmia is highest when cardiac monitoring devices are applied early after syncope, ideally at the index visit **[9-11]**. The

SYNARR-Flash study **[10]** was the first international, multicentre, prospective trial designed to evaluate the feasibility and usefulness of external prolonged ECG monitoring in the early clinical work-up of unexplained syncope. It showed that the yield for detecting a diagnostic event during a 4-week external ECG monitoring period was greater when a device was placed during the first 15 days after an index event than when placed more than 15 days afterwards (OR 6.2, 95% CI 1.3-29.6, p=0.021). The recently published validation study of the Canadian Syncope Rule Score **[11]** showed that almost all (91.7%; 176 of 192 outcomes) arrhythmic outcomes experienced by medium and high-risk patients were identified within 15 days of the index ED syncope presentation.

The recent European Society of Cardiology (ESC) syncope guidelines **[3]** have recommended an enhanced role for prolonged ECG monitoring when arrhythmic syncope is suspected. In order to solve the problems of currently available routine ECG monitoring devices such as Holter and ILR, several novel ambulatory cardiac monitoring devices have recently been developed [e.g. BG Mini (Preventice) **[12]**, ZIO®XT Patch (iRhythm) **[9,13,14]**, Carnation Patch (Bardy) **[15]**, Bittium Faros 180/360 (Bittium Faros/Technomed **[15]**), myPatch-sl (DMS)]. Such devices hold a lot of potential, as they are non-invasive, water-resistant, have no leads or wires, are discreet to wear and are CE-marked for clinical use in the UK. They continuously monitor the heart for up to 14 days including during sleep, in the shower, and during moderate exercise and some have a button for patients to capture symptomatic events. At the end of the monitoring period patients return the devices back to the company (by mail) or NHS (to be downloaded) for analysis which can be done in house or by the company. These devices are easy to apply at the point of presentation with syncope. They offer medium duration high fidelity ECG recording and are well tolerated **[16,17]**, ECG data quality is excellent and compliance returning the device is good (generally <3% loss). A National Institute for Clinical Excellence (NICE) guidance medtech innovation briefing [MIB101] published in 2017 looking at current evidence for one such device suggested it could be used for monitoring over 14 days as well as, or instead of conventional Holter or event recording monitoring **[13]**.

1.1.3 Existing Literature

The utility of external prolonged ECG monitoring in the work-up of syncope is still undefined. With a growing number of novel ambulatory cardiac monitoring devices available on the market it is vital that well designed studies drive changes in clinical practice rather than innovative technology being adopted early into clinical settings without the accompanying evidential background. Recent NICE draft guidance from a medical technology evaluation of one such device, the Zio XT **[14]** recommended research to address uncertainties about the resource use associated with monitoring compared with standard care; in particular the numbers of outpatient visits and repeat tests needed.

A search of clinicaltrials.gov demonstrates that only one study in this area is currently ongoing internationally **[18]**. The REMOSYNC study led from Ottawa, is comparing two monitoring devices placed prior to ED discharge. A device called Cardiophone (live monitoring device) is the intervention arm and a Mobile Cardiac Telemetry device which functions as a Holter for first 48-hours and then as an event recorder (days 3-15) for dysrhythmia is the control arm **[18]**. Neither of these strategies are standard care in the UK. Furthermore, the study prioritises the detection of dysrhythmia rather than the more important impact of ambulatory monitoring on patient care and cost effectiveness, as highlighted in the James Lind Emergency Medicine Research Priorities **[19]**.

In identifying this growing need in the evidence base for such devices, the Emergency Medicine Group of Edinburgh (EMERGE) completed a single-centre, prospective, cohort pilot study (PATCH-ED) **[9]**. Patients 16 years or over presenting to the ED, whose syncope remained unexplained after assessment were fitted immediately with 14-day ambulatory ECG monitoring (ZIO®XT Patch). A significant dysrhythmia was detected in 3 in 10 patients (with 1 in 10 being symptomatic and serious) and a diagnostic finding was detected in 3 in 4 patients (up to 75% of patients). In addition, the blinded PATCH-ED report review suggested that the monitor would

significantly reduce requirement for standard outpatient ambulatory ECG monitoring from 80% to 5%.

The limitations to the few published studies on ambulatory monitoring in syncope patients is that they are generally single centre without any comparative group with heterogeneous patient populations and device capabilities **[10]**. This is problematic as syncopal recurrences often decrease spontaneously after medical assessment, even in the absence of a specific therapy **[3]**. In general, syncope recurs in around 50% of patients within a year and episodes may decrease by as much as 70% compared with the preceding period **[3; Sup Table 10]**. Several potential explanations have been provided for this including patient education in syncope aborting manoeuvres and ensuring hydration (if a postural element) **[3]**. The consequence of this spontaneous decrease is that any therapy for syncope prevention appears to be more effective than it actually is. For this reason, observational data is questionable and an RCT trial is required.

1.1.4 Trial Design

The ASPIRED randomised controlled trial (RCT) will compare a novel ambulatory cardiac monitoring device with standard practice in syncope patients.

The PATCH-ED pilot study helped establish trial methods and numbers of available participants informing this RCT **[9]**. This pilot study showed a novel ECG monitoring device was able to detect serious cardiac dysrhythmia requiring treatment in a significant proportion of patients (and are not just detecting incidental rhythms of no clinical relevance) and possibly up to 75% of patients receive a diagnosis. It also demonstrated the potential to influence clinical management decisions relating to hospital admission and participant outcomes. Whilst there was no increase in mortality in the PATCH-ED pilot study compared to a historical cohort, this RCT will instigate a Data Monitoring Committee (DMC) to monitor adverse events in intervention group participants who would normally be admitted to hospital but are discharged home. If this strategy is adopted by some clinicians this should not affect the outcome adversely as there are no research papers showing hospital admission improves outcome in syncope **[20]**.

1.2 RATIONALE FOR STUDY

1.2.1 Importance of the Question

Diagnosing underlying dysrhythmia in ED syncope patients is difficult. There is evidence that diagnostic yield for detecting underlying dysrhythmia is highest when cardiac monitoring devices are applied early, ideally at the index visit.

This research study hypothesises that applying cardiac monitoring early after syncope at the index visit is the optimum strategy to detect, diagnose, treat and exclude underlying cardiac dysrhythmia.

1.2.2 Current Treatment Options

Diagnosing underlying dysrhythmia in ED syncope patients is difficult. Patients have often recovered from their syncopal episode and have normal ECG's. In the absence of a diagnosis, these patients are commonly referred to syncope clinics where ambulatory monitoring devices may be applied as per ESC syncope guidelines **[3]. T**hese devices are often problematic for patients and achieve low diagnostic yields.

Evidence evaluating the feasibility and usefulness of prolonged ECG monitoring in the early work-up of unexplained syncope is however still in its infancy. It is unclear for example how long patients selected for ambulatory ECG monitoring should be monitored. PATCH-ED was the first study to compare novel ambulatory cardiac monitoring with standard practice in patients with unexplained syncope. This study highlighted the greater diagnostic potential for medium

duration ambulatory monitoring applied early after syncope. This wider scale study is now required to provide the evidence for centres to confidently adopt this new technology into clinical care knowing it could reduce episodes, recurrence, hospital admission and healthcare costs and that it is reliable and safe.

1.2.3 Study Intervention

This is a UK open prospective parallel group multicentre RCT of an immediate 14-day ambulatory patch heart monitor versus standard care monitoring in 2234 participants presenting acutely with unexplained syncope. The patient focussed primary endpoint will be number of episodes of syncope at one year.

1.2.4 Measurement of Outcomes

An early ambulatory monitoring strategy has the potential to change current syncope management from low diagnostic yield Holter to higher yield ambulatory monitoring, reduce episodes of syncope, reduce risk of recurrence and its potential serious consequences, reduce hospital admissions, reduce overall health costs and increase quality of life by allowing earlier diagnosis, treatment and exclusion of clinically important dysrhythmias.

This proposed strategy will inform practice changing guidelines in the early management of unexplained syncope, including ESC, American College of Cardiology (ACC), NICE and Scottish Intercollegiate Guidelines Network (SIGN) by providing evidence of improved outcomes for patients and reduced health care costs when monitoring devices are applied early after syncope.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine whether immediate, enhanced (14-day) ambulatory ECG monitoring decreases the number of self-reported episodes of syncope at one year compared to standard care monitoring in acute unexplained syncope patients.

2.1.2 Secondary Objectives

To determine whether immediate, enhanced (14-day) ambulatory ECG monitoring in acute unexplained syncope patients can:

1. Decrease the number of episodes of self-reported syncope at 90 days, and 2 years compared to standard care monitoring.
2. Decrease the time to detection of clinically significant cardiac dysrhythmia compared to standard care monitoring.
3. Increase the rate of detection of clinically significant cardiac dysrhythmia at 90 days and 1 year compared to standard care monitoring.
4. Increase the rate of ECG/symptom correlation at 90 days and 1 year compared to standard care monitoring.
5. Demonstrate cost effectiveness compared to standard care monitoring.
6. Decrease the number of episodes of syncope identified in the medical records at 90 days, 1 and 2 years compared to standard care monitoring.
7. Decrease the index hospital admission rate and duration of hospital stay compared to standard care monitoring
8. Decrease 90 days, 1- and 2-year syncope recurrence rates (identified in the medical records and self-reported) compared to standard care monitoring

9. Increase patient satisfaction compared to standard care monitoring
10. Decrease the rate of 30 day, 1 and 2 year all cause death compared to standard care monitoring
11. In the intervention group, by reporting the timing of detection of clinically significant cardiac dysrhythmia what is the optimum duration of acute ambulatory ECG monitoring
12. Increase the affect rate of diagnostic testing and therapeutic intervention.

As the intervention may lead to reduced index admission rates and shorter duration of hospital stay through clinicians becoming more confident to discharge patients without prolonged inpatient monitoring, 30-day mortality will be part of the standard DMC reporting.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Number of self-reported episodes of syncope at one year.

2.2.2 Secondary Endpoints

1. Within trial cost effectiveness (cost per syncope avoided and cost per quality adjusted life year [QALY] gained), and lifetime cost per QALY at 2 years and if appropriate at 1 year.
2. Number of self-reported episodes of syncope at (a) 90 days and (b) 2 years, those identified in the medical records at (c) 90 days, (d) 1 year and (e) 2 years, and syncope recurrence rate at (f) 90 days, (g) 1 year and (h) 2 years
3. Index presentation hospital (a) admission rate and (b) duration of hospital stay
4. Patient Satisfaction (measured using a patient questionnaire) at 1 year
5. Clinically significant cardiac dysrhythmia (Serious and/or symptomatic cardiac dysrhythmia **Table 1**) at (a) 90-days, (b) 1 year and (c) 2 years.
6. (a) 30 day, (b) 1 year and (c) 2 year all cause death
7. Detection of diagnostic ECG/symptom correlation (symptomatic) at (a) 90-days, (b) 1 year and (c) 2 years.
8. Time to detect clinically significant cardiac dysrhythmia (i.e. time to clinician being aware)
9. In the intervention group, duration of enhanced ambulatory ECG monitoring required to detect clinically significant cardiac dysrhythmia
10. Number and type of diagnostic tests and therapeutic interventions at (a) 1 year and (b) 2 years

2.2.3 Table 1: Definitions of clinically significant cardiac dysrhythmias

Ventricular Fibrillation (VF) *
Ventricular Tachycardia (VT) ≥120 beats per minute (bpm) for ≥30 seconds *
VT ≥120 beats per minute for <30 seconds (≥4 beats) *
Complete or 3rd degree heart block *
Second degree atrioventricular heart block Mobitz type II *
Second degree atrioventricular heart block Mobitz type I
Pause ≥6 seconds *
Sinus pause ≥2.5 seconds when awake or ≥4 seconds at night (but <6 seconds)
Sinus bradycardia <30 beats/minute *
Bradycardia <40 beats per minute for ≥30 seconds *
Bradycardia <40 beats per minute for <30 seconds

Sick sinus syndrome with alternating sinus bradycardia and tachycardia
Junctional / idioventricular rhythm ≥30 seconds in duration
Supraventricular tachycardia >100 beats per minute ≥30 seconds in duration
Atrial flutter/fibrillation with ventricular rate >100 bpm or <60 bpm ≥30 seconds in duration
New Atrial flutter/fibrillation ≥30 seconds in duration

* Defined as 'Serious' clinically significant cardiac dysrhythmia

Nb. All dysrhythmias will also be classed as symptomatic or asymptomatic during monitoring period

3 STUDY DESIGN

P: Population	Adults presenting acutely to UK hospitals with syncope remaining unexplained after initial ED/AMU assessment
I: Intervention	14-day ambulatory heart monitor placed on patients
C: Comparator	Standard care monitoring
O: Primary Outcome	Number of self-reported episodes of syncope at one year

ASPIRED is an open prospective parallel group randomised controlled trial of a 14-day ambulatory heart ECG monitor applied to patients versus standard care in patients presenting acutely with unexplained syncope.

Recruitment will take place in ~35 NHS acute tertiary and district hospitals.

Participants will be randomised, 1:1, between the two study arms.

Randomisation will be performed using a web-based randomisation service to ensure allocation concealment, managed by ECTU. The allocation sequence will be created by an ECTU database programmer using computer-generated pseudo-random numbers.

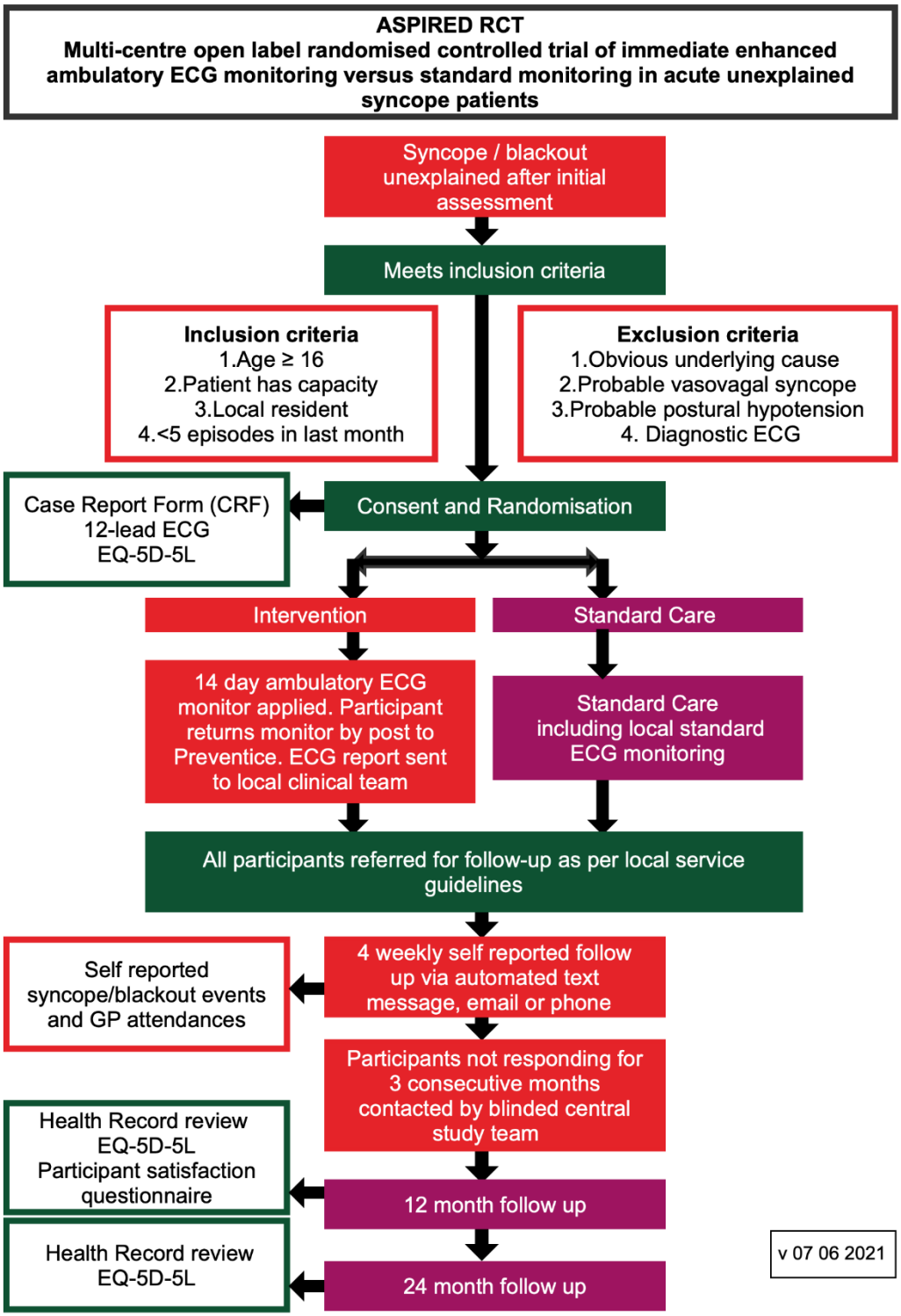
Stratification by site will be used to ensure balanced randomisation. Stratification by other site-level characteristics will not be performed.

Standard care will include all care usually given to unexplained syncope patients at each participating site along with some form of standard care monitoring such as but not limited to wired inpatient telemetry, Holter style monitoring or implantable loop recorder.

The study will be conducted over 4 years. Recruitment will take place over 24 months. Intervention group participants will be fitted with a 14-day ambulatory heart monitor. All participants will be followed-up for 2 years after index event.

A blinded sample size review will take place after approximately 50% of participants have been randomised to ensure that the trial achieves the required statistical power.

3.1 Schematic diagram of the study design (Figure 1)



4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

2234 adult (16 years or older) participants presenting acutely to UK hospitals with syncope remaining unexplained after initial ED/AMU assessment.

Syncope will be defined as transient loss of consciousness (TLoC) with inability to maintain postural tone and immediate complete spontaneous recovery without medical intervention **[23]**.

4.2 INCLUSION CRITERIA

1. Syncope remains unexplained after initial ED/AMU assessment.
2. Aged ≥ 16 years
3. Patient has capacity
4. Local resident (i.e. resident within local health board so will not be lost to medical record follow up)
5. <5 self-reported episodes of syncope in the previous month

4.3 EXCLUSION CRITERIA

1. Obvious underlying cause after assessment
   a. Features of vasovagal syncope **(see Table 2) AND** absence of structural heart disease **AND** normal physical examination **AND** normal ECG
   b. Dysrhythmia on pre-hospital or hospital ECG as likely cause of syncope
   c. Postural hypotension (symptomatic postural drop >20 mmHg **AND** suggestive history)
   d. Confirmed diagnosis of Pulmonary Embolus or Acute Myocardial Infarction
   e. Radiological diagnosis or clinical signs/symptoms of cerebrovascular accident/transient ischemic attack or subarachnoid haemorrhage
   f. TLoC secondary to:
      i. Haemorrhage
      ii. Alcohol or illicit drugs
      iii. Epileptic seizure
      iv. Hypoglycemia
      v. Head trauma
      vi. Other obvious cause of syncope as presumptive cause of TLoC
2. Inability to consent
3. Previous recruitment into the study
4. Patient in custody or prison
5. Aged <16 years
6. Patient does not reside within local health board and will therefore be lost to medical record follow up
7. 5 or more self-reported episodes of syncope in previous 4 weeks

Pregnancy **is not an** exclusion criteria.

4.3.1 Table 2: Features of vasovagal / postural syncope

Associated with typical symptoms of reflex syncope (e.g. light-headedness, feeling of warmth, nausea, vomiting)
After sudden unexpected unpleasant sight, sound, smell, or pain
In association with micturition, defaecation, cough, laughter, venepuncture, blood phobia
After prolonged standing or crowded, hot places
During a meal or after eating a meal
With head rotation or pressure on carotid sinus (e.g. tumour, shaving, tight collars)
Associated with standing up quickly from a sitting or lying position
Long history (years) of recurrent syncope with low-risk features with the same characteristics of the current episode

4.4 CO-ENROLMENT

Co-enrolment will be permitted to CTIMPs and non-CTIMPs where this does not affect the ASPIRED study randomisation allocation, outcome measure assessment, and where doing so is not expected to burden the participant in line with the Sponsors co-enrolment policy.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential participants will be identified from ED/AMU departments or other acute settings and approached either during their stay in ED/AMU or during their hospital stay. Patients discharged from ED/AMU will be identified using electronic medical records or through referral from the clinical team and approached during their hospital stay.

Potential participants who are not approached during their stay in hospital (e.g., they attend out of hours and are discharged from ED/AMU, lack of study team availability or have a short hospital stay) will be identified using electronic medical records or through referral from the clinical team and contacted by phone by the research team to invite them to take part in the study. Any member of the clinical team who has received general and trial specific training may also identify participants in this way.

Research staff participating in patient identification should be a part of the clinical team responsible for or contributing to the patient's care. If research staff are not considered to be part of the direct care team locally, activities carried out prior to consent (including identification and introduction to the study) will be carried out by a member of the direct care team. Where research staff are not considered to be part of the care team, the research team 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

A log will be kept of patients who were approached to take part in study and subsequently found to be ineligible or not recruited.

5.2 CONSENTING PARTICIPANTS

Potential participants will be given a Participant Information Sheet (PIS), which will explain the aims of the trial and the potential risks and benefits of participating in the study.

Depending on research staff, or appropriately trained delegate availability, patients who are willing to take part will either be consented within the ED/AMU or other acute hospital setting or contacted by a member of the research team by telephone after discharge to discuss possible participation in the trial.

Recruitment will be as soon as possible after the initial presentation. Patients will be given enough time to consider the study and ask questions regarding their participation. In the context of consent in acute settings, this is likely to be at most up to an hour. Potential participants will receive adequate oral and written information and opportunity to ask questions.

Patients who are consented when in hospital will be asked to provide written informed consent.

Patients who are contacted by telephone will be given the option to either:

- attend a study visit (travel expenses provided) to provide written informed consent in person, or
- provide informed consent verbally over the telephone

Patients who have provided informed consent verbally over the telephone will have a written consent form signed and witnessed by the research member on the patient's behalf. This signed form will be sent to the patient with contact details of the research team should they decide to withdraw consent.

If any potential participant does not respond after up to 3 phone calls, then no further attempts will be made to contact them.

Capacity will be assessed by the research team or a clinician responsible for the treatment of the participant. The trial excludes patients who have "inability to give informed consent" and therefore patients with temporary incapacity due to their current illness or with permanent incapacity will not be recruited.

Potential participants will be approached in hospital or contacted by the clinical team and offered participation in the study, recruited and randomised within 72 hours of their hospital attendance to the ED/AMU. It is important that patients who present to hospital when a member of the local study team is not available, are not disadvantaged by not being offered the opportunity to take part in research. This approach is to enable as many patients as possible who wish to take part in the research, the opportunity to take part in the study. This has previously been approved by Research Ethics Committees (e.g. TARGET-CTCA).

If these patients are still hospitalised, they can be approached by the local clinical team or research team if part of the clinical team. Consent, randomisation and intervention or standard care can then be arranged by the research team at the time.

If a patient has been discharged from hospital, then they will be contacted by the local clinical team or research team (if part of the clinical team), and a copy of the PIS will be emailed or posted out to the patient. The PIS will also be available on the trial website. If the patient wishes to participate, a delegated member of the local study team will verbally consent the patient over the telephone and will sign the consent form on behalf of the participant. The original consent form will be filed in the ISF and the participant will be sent a copy of this document. A copy will be filed in the participant's medical notes. Alternatively the patient can attend a study visit with travel expenses provided if required, to provide written informed consent in person.

The ambulatory ECG device can also be sent to the participant's chosen address or collected from the local study team, whichever is easiest for the participant if randomised to the intervention arm.

Neither participants nor treating clinicians will be blinded to allocation.

5.2.1 Screening Log

Each participating centre will upload screening information of non-identifiable potentially eligible patients who were approached to participate in the study, onto the study database. This will be analysed to assess whether the recruited participants are representative of the potentially eligible population, and whether there are regional or temporal differences in participant recruitment. In patients identified to have syncope which remains unexplained after initial ED/AMU assessment who are not recruited to the study, reasons will be documented.

5.2.2 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form (eCRF), if possible. We will request clarification of which part(s) of the trial that the participant wishes to withdraw from. Data collected up to the point of withdrawal will be retained. Passive follow-up from routine hospital electronic healthcare records will continue unless the participant withdraws from this. To safeguard rights, the minimum personally identifiable information possible will be collected.

30-day mortality will be part of the standard DMC reporting. If there is a statistically significant (one-sided 2.5% significance level) increased 30-day mortality in the intervention group, the study will be discontinued.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

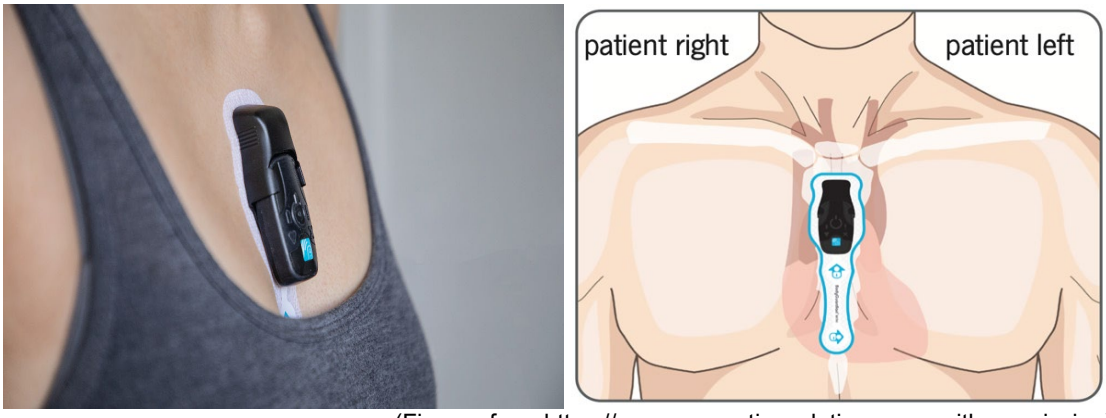
Assessment	Screening	Day 1 baseline	Monthly	90 days	Every 3 months	1 year	2 years
Window of time for evaluation	**n/a**	**n/a**	**+/- 14 days**	**+/- 14 days**	**n/a**	**+/- 30 days**	**+/- 30 days**
Assessment of Eligibility Criteria	☒						
Informed consent	☒						
eCRF completion including demographic data and contact details	☒						
Routine clinical care (e.g. ECG)	☒						
Randomisation		☒					
Intervention group participants fitted with a 14 day ambulatory heart monitor		☒					
Referral for syncope assessment and standard care monitoring as per local service protocol to be seen ideally within 4-6 weeks of the index event especially if discharged from ED or if this did not occur during index admission.		☒					
EQ-5D-5L questionnaires		☒				☒	☒
NHS resource utilisation data from routine hospital electronic healthcare records extracted by the local study team)				☒		☒	☒
Participant contacted on a 4-weekly basis via automated text message, email or phone with a link to a brief web based questionnaire asking for the number of syncope events experienced since last response, and the number of GP attendances for any reason.			☒				
Participants not responding for 3 consecutive months will receive a phone call from the central study team (blinded to participant's study arm allocation) to collect missing data, ensure no syncope episodes have occurred and to encourage continued future engagement. Participants with a mean of 5 or more episodes/month will also receive a phone call from the central study team (blinded to participant's study arm allocation) to ensure that participants are recording true syncope events and are seeking appropriate medical advice.					☒		
Participant satisfaction questionnaire						☒	

Participants will have an eCRF completed at randomisation, comprising demographic, historical and examination characteristics, Canadian Syncope Risk Score (recording troponin only if measured), ROSE rule positive/negative, 12-lead ECG, and disposition (admission/discharge). Participants contact details (email and contact phone number) will be confirmed along with preferred method of self-reporting of further episodes (text or email). Participant disposition (i.e., admission/discharge) will be at the discretion of the treating clinician.

All recruited participants regardless of allocation group, will be referred for syncope assessment as per local service protocol (e.g., cardiology /general medicine/ syncope specialist /ambulatory care) to be seen ideally within 4-6 weeks of the index event especially if the participant was discharged directly from the ED or if syncope assessment did not occur during the participant's index admission. Subsequent investigation should be arranged at the discretion of the treating clinician, based on local guidance and the participant's history and frequency of TLoC. NICE guidance **[21]** recommends for participants who have frequent TLoC this is likely to be Holter monitoring and extended ambulatory monitoring with event marker for less frequent symptoms, with implantable loop recorder (ILR) reserved for second line investigation. We will monitor standard care at each site and compare this with NICE guidance.

Participants randomised to the intervention arm will be fitted with a 14-day ambulatory heart monitor (Preventice BodyGuardian Mini) applied by the study team as soon after ED attendance and randomisation as possible. Some sites may choose the option of sending out the ambulatory heart monitor to participants (after consent) who were not recruited during their initial hospital visit. It is recognised that if late recruitment and randomisation occurs (i.e. close to 72 hours after ED/AMU attendance), ambulatory heart monitor placement may be up to a few days after index hospital visit. Participants will be registered on the Preventice UK portal by study number and their allocated patch number only. No patient identifiable information will be passed to Preventice UK.

The ambulatory ECG monitor will be placed on the participant's chest wall over the sternum (middle bony area of chest). It is connected directly to an ECG electrode sticker (see **figure** below). It is the size of a watch face, is non-invasive, water-resistant and is discreet to wear. It continuously monitors the heart for up to 14 days including during sleep, in the shower, and during moderate exercise. It does not impact on activities of everyday life such as showering, swimming and other exercise, or a participant's choice of clothes especially in warmer weather, as it sits comfortably underneath these. The participant's skin does not require shaving but is cleaned prior to attaching the device, which are easily removed by the participant after 14 days. The monitor can be worn by both women and men.



(Figures from https://www.preventicesolutions.com with permission)

Participants will be required to press the button on the heart monitor after the episode, in the event of them having a syncopal event whilst wearing the heart monitor. They will also be

required to complete a paper symptom diary that records when symptomatic episodes occurred.

The participant will wear the ambulatory ECG monitor for a maximum of 14 days after which they will simply remove the ambulatory ECG monitor and return it in a pre-paid envelope to Preventice UK. No identifiable patient details will be sent to Preventice. The monitor will be reported by an ECG technician and Preventice UK will share the reported ECG identified by study number with the participant's local study team. When the 14-day ambulatory heart monitor report is returned to the local study team, a front page will be added to the report by the local study team confirming participant details prior to release to the treating clinician/team, and if local protocol, placement in the participant health record. Each site will be expected to detail prior to commencing the study, to whom they wish the intervention ECG report to be returned to (i.e., follow-up clinic lead clinician, clinician to whom the participant has been referred, named cardiologist etc).

The participant's GP will be informed that the participant has been enrolled in the study. All participants will have hospital follow-up and therefore the participant's GP will be informed of the results of any ECG investigations via routine hospital clinical correspondence.

Participant will be advised in the PIS that all participants will have hospital follow-up and that they will be informed of the results of any ECG investigations via this route, or via routine hospital clinical correspondence.

Any study participant with a serious dysrhythmia **[3]** on the ECG report **(See Table 1)** will be contacted as soon as possible by the local team and managed appropriately according to local policy. This process worked well in our pilot study. Treatment of device findings will be at the discretion of the treating clinician at each site.

Echocardiography will be considered in both groups at the discretion of the treating clinicians but would likely only be required for participants who have suspected cardiac syncope and no echo in the previous 12 months, and history/physical exam/ECG features suggestive of structural/valvular heart disease or heart failure (likely ~5% of study participants).

6.2 LONG TERM FOLLOW UP ASSESSMENTS

All participants will be followed up for two years from randomisation through hospital records, questionnaires and participant reported events.

Participants will be contacted at monthly intervals throughout the study follow-up which will last for 2 years, by automated text or email (participant preference) with a link to a brief web-based questionnaire asking for the number of syncope events experienced since their last response and how many of these they attended hospital for. Those who are unable to access digital forms of communication will receive phone calls.

They will also be asked since their last response how many times they have visited their GP practice for any reason including all face-to-face, telephone and online consultations. We will not collect GP visit data directly from healthcare records or directly from GP practices.

Participants with a mean of 5 or more episodes/month will also receive a phone call from the central study team (blinded to participants study arm allocation) to ensure that participants are recording true syncope events and are seeking appropriate medical advice.

Participants will also be contacted at one and two years by the central study team (blinded to participants study arm allocation) to complete a quality-of-life questionnaire. The one- and two-year reminders will open one or two years after index attendance +/- 30 days. In the event of non-response, participants will be contacted on up to 3 occasions. The participants' involvement in the study will cease at 2 years.

7 DATA COLLECTION

Participants will have an eCRF completed at randomisation by the **local study team.**

Endpoint data including NHS resource utilisation will be extracted by the **local study team** from routine hospital electronic healthcare records at 90 days, 1 and 2 years and will be entered into a bespoke database designed by Edinburgh Clinical Trials Unit (ECTU). This will be complemented by participant endpoint data collection.

All participants will be contacted on a 4-weekly basis +/- 14 days for a duration of 2 years via automated text message or email (whichever they prefer) with a link to a brief web-based questionnaire asking for the number of syncope events experienced since their last response and how many of these they attended hospital for. Those who are unable to access digital forms of communication will receive phone calls. They will also be asked since their last response how many times they have visited their GP practice for any reason including all face-to-face, telephone and online consultations. This will import directly into the central ECTU study database. This patient reported data will be used to inform the primary endpoint.

The small number of participants unable to access digital forms of communication, participants not responding for 3 consecutive months, and participants recording multiple episodes of syncope (5 or more self-reported episodes of syncope in a one month period), will receive a phone call from the central study team (blinded to participant's study arm allocation) to collect missing data, ensure no syncope episodes have occurred and to encourage continued future engagement.

Our experience from the IPED study **[22]** and other work is that digital forms of communication are very acceptable to those at least up to the age of 75 (70% of our proposed participants will be 75 or less) **[22,23]**.

All participants will be asked to complete EQ-5D-5L questionnaires at baseline, 1 and 2 years by post or email depending on patient preference, and to identify the level of social care they require (e.g., fully independent, using alarm, regular social care visits, residential care). The 1 year EQ-5D-5L questionnaire will also be accompanied by a participant satisfaction questionnaire.

ECTU will collect and clean primary data and perform primary and secondary analyses.

The anonymised electronic healthcare record data will be sent to Sheffield to apply unit costs and tariffs, to estimate within trial costs and QALYs, and then to undertake lifetime economic modelling.

7.1 Source Data Documentation

Source data plans will be created to indicate where protocol required information will be originally documented. Source data worksheets created by the ECTU will be made available.

Data collected via text, phone call or emails from participants, and endpoints will be entered directly onto the eCRF.

7.2 Case Report Forms

Participants will have an eCRF completed at randomisation, comprising demographic, historical and examination characteristics, Canadian Syncope Risk Score, ROSE rule positive/negative, 12-lead ECG, and disposition (admission/discharge). Participants contact details (email and contact phone number) will be confirmed along with preferred method of self-reporting of further episodes.

8 DATA MANAGEMENT

8.1.1 Personal Data

The following personal data will be collected as part of the research:

- Participant's name, address, telephone contact, email, date of birth, ethnicity and General Practitioner details will be inputted and stored on the specially designed online study eCRF. Local study teams will only be able to access their own participant's information.

We will seek participant consent to store patient identifiable data for up to 15 years at local sites in order that it may be used for future ethically approved studies (likely long term follow-up studies) which may involve recontacting study participants, as well as accessing their routine hospital electronic healthcare records.

Community Health Index (CHI) number, NHS number, hospital number or other identifying unique hospital identifier will be recorded by the local research team, on the eCRF, alongside the unique study identification number allocated at randomisation and will also be inputted and stored on the specially designed online study electronic database.

Personal data will be stored by each local research team in a secure location according to local NHS/University policies, as applicable. Paper copies will be filled in a locked drawer with limited numbers of staff with access. Electronic study documents will be stored on a specially designated password protected drive/computer with password protected database on a shared drive with limited access. Consent forms will be stored securely in a locked office.

Anonymised study data and metadata will be preserved for future reuse for a minimum of 3 years from the protocol defined end of study point. Where participant consent has been given, patient identifiable data will be stored at local sites for up to 15 years.

Baseline and follow up medical record endpoint data will be collected by the **local study team** at each site. Data sources include participants' electronic patient records, investigation reports and through interaction with the participant as part of clinical care. This will be inputted by the local study team and stored on the specially designed online study electronic database.

The participant reported 4 weekly web based questionnaire will import directly into the online study electronic database. Responses from participants receiving phone call follow-up from the **central study team** (blinded to participant's study arm allocation) will be entered into the online study electronic database by the central study team.

Access to collated participant data will be restricted to individuals from the local study team treating the participants, ECTU and the University of Edinburgh clinical research team, representatives of the sponsor and representatives of regulatory authorities.

8.1.2 Transfer of Data

Identifiable data collected by the study will not be transferred to any external individuals or organisations outside of the sponsoring organisations. After publication of the aggregated ASPIRED trial data, individual de-identified participant data (including data dictionaries) will be available upon request to ECTUdatashare@ed.ac.uk in accordance with the ASPIRED Study Data Sharing Plan.

No patient identifiable information will be transferred to Preventice Solutions/ Preventice UK. All participants will be identified by their unique study identification number.

8.1.3 Data Controller

The University of Edinburgh and NHS Lothian will be joint data controllers.

8.1.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

9.1.1 Proposed sample size

2234 participants (1117 in standard and 1117 in intervention) presenting acutely with syncope whose syncope remains unexplained after initial ED/AMU assessment will be recruited.

Overall syncope volume based on ED volume at centres with 'in principle agreement' is estimated to be 43,500 syncope presentations per annum (1-2% of 2.9M ED attendances in 26 sites).

9.1.2 Power calculation

Using an estimated mean 1-year recurrence rate in untreated patients of 42.5% **[3; Sup Table 10]** and a reduction in 1-year recurrence rate to 10% in patients who are treated **[8,24]** then the hypothesis is a 1-year recurrence rate in the standard group (2% diagnosed with a symptomatic significant arrhythmia with 90% of these expected to not have recurrence after treatment) of 40.7% compared to a recurrence rate of 33.1% in the treatment group (10.5% of pilot participants diagnosed with symptomatic significant arrhythmia at 90 days with 90% of these expected to not have recurrence after cardiac arrhythmia treatment) equating to an event rate ratio of 0.81. A more conservative effect size of 6% (40% vs 34%) will be assumed corresponding to a more conservative event rate ratio of 0.85. A large study of unexplained untreated syncope patients **[25]** suggests a median (IQR) number of events in the preceding 2 years of 3 (2-4) with a median (IQR) per year of 2 (1-3.5). The ESC Guidelines **[3]** suggest that the number of events has a good fit to a Poisson distribution and the untreated event rate post-attendance is about 70% reduced from the pre-attendance rate. The ESC guidelines **[3]** and PICTURE **[25]** suggest a mean number of events per participant of approximately 1 during 1 year of follow-up. If we assume that this follows a negative binomial distribution (which allows for "over dispersion" versus the Poisson distribution) then a study of 1064 participants per group would have 90% power (two-sided significance level=5%, over dispersion=0.25) to detect an event rate ratio of 0.85.

To explain the event rate calculation in more detail: In a nominal 10,000 intervention group population, 4250 patients will be expected to have a 1-year recurrence if untreated **[3]**. If we subject these 10,000 patients to our intervention, we expect to make an important treatable cardiac dysrhythmia diagnosis in 1050 patients. These patients will be among the 4250 with a 1-year recurrence having had a recurrence within 1 year which the intervention detected. Of these, after treatment, only 10% will have further recurrence (i.e., 105 patients). Therefore, the number of patients in the intervention group in whom further recurrences are prevented is 90% of 1050 patients, i.e., 945 patients. The number of patients with recurrence in the intervention group is therefore reduced by 945 patients i.e., 3305 patients. Those patients not having recurrence will not benefit from the intervention (as the intervention can only benefit those with positive monitoring during the follow up period). If we take a nominal 10,000 standard care

population, 4250 patients will be expected to have a 1-year recurrence if untreated. If we subject these 10,000 patients to standard care, we expect that we will make an important treatable cardiac dysrhythmia diagnosis in around 200 patients. Of these only 10% will have further recurrence (i.e. 20 patients). Therefore, the number of patients in the standard care group in whom recurrence is prevented is 90% of 200 patients, i.e. 180. The number of patients with a recurrence in the standard care group is therefore reduced by 180 patients i.e. 4070 patients. The intervention benefit is therefore expected to be 765 per 10,000 (4070 minus 3305). Our power calculation has assumed a more conservative intervention benefit (600 per 10,000 rather than 765 per 10,000) corresponding to an event rate ratio of 0.85 rather than 0.81.

To verify the assumptions regarding the primary outcome event rate and the level of overdispersion in the distribution of event counts, the Trial Steering Committee will undertake a blinded sample size review after 50% of participants have been randomised. A negative binomial model will be fitted to pooled primary outcome data from both randomised groups, generating estimates of the overall primary outcome event rate and the shape parameter (which reflects the level of overdispersion). These will then be inserted in the standard sample size formula for an outcome with a negative binomial distribution to obtain the revised sample size estimate. The study target sample size will only be revised in the event that blinded re-estimation suggests an increase in sample size in order not to limit power for key secondary outcomes. Friede and Schmidli (2010) **[26]** demonstrate that such an approach does not inflate the type I error and ensures that study attains its planned statistical power. On average, a small increase in sample size is required to achieve this. The study sample size has not been inflated for the single interim futility analysis because this analysis will likely take place when the number randomised is close to the overall target sample size, there is a negligible chance of wrongly stopping for futility in the scenario where a significant benefit of the intervention would have been identified if recruitment had continued to the full sample size. The inclusion of the futility analysis therefore has minimal impact on the statistical power of the trial

9.1.3 Compliance and loss to follow up

The study will recruit an extra 5% in each arm (i.e. 1117 participants per arm; 2234 in total) to allow for drop-out/loss to follow up although we expect this to be low (<1% in pilot) and drop out due to death (<1% in pilot). It is expected that most people will respond to some text/email follow-ups, but few will respond to all. We will therefore call any participant who has not responded for 3 consecutive months to ensure no syncope episodes have occurred and to encourage continued future engagement. Participants will be defined as lost to follow up only if both one-year electronic patient health record data and one year self-reported data is unavailable.

9.2 PROPOSED ANALYSES

9.2.1 Statistical analysis

The primary outcome, number of self-reported episodes of syncope in the 12 months following randomisation, will be analysed by negative binomial regression. The primary outcome event rate ratio (14-day ambulatory heart monitor vs standard care) will be reported with its 95% confidence interval. An offset term for follow-up duration will be included to account for participants with partial follow up.

The secondary outcomes for the number of syncope episodes at 90 days and 2 years, will be analysed similarly. Binary secondary outcomes will be analysed by logistic regression, reporting the odds ratio (14-day ambulatory heart monitor vs standard care) and its 95% confidence interval. Full details of analysis, including the estimand(s) of interest and methods for handling missing data, will be written into a Statistical Analysis Plan, which will be finalised prior to database lock without knowledge of the unblinded treatment allocations. There are no planned subgroup analyses.

9.2.2 Bias

The primary outcome is a quantitative endpoint (number of syncope episodes) collected through automated participant reporting (text or email). The automated participant reporting will import directly into the ECTU central study database to reduce reporting bias. Central research staff who phone participants will be blinded to participant allocation.

There is a small potential for bias in assessing secondary outcomes due to the difficulty in blinding electronic patient health records when reviewed by research staff. This has been reduced by making the endpoint data collection from electronic patient health records as objective and structured as possible. Secondary endpoints such as cardiac dysrhythmia and diagnostic symptom/ECG correlation will be reported by the local treating clinician using an objective structured approach.

The study analysis methods will be written into a pre-specified Statistical Analysis Plan by Professor Christopher Weir from ECTU, prior to access to unblinded trial data. Analysis will be performed on an intention to treat basis.

This is a pragmatic study. By including many centres with subtle variations of standard care we expect to improve applicability and likelihood of adoption of positive study findings. We will record data on usual care in the study, to aid interpretation of the study findings.

9.2.3 Cost Effectiveness Analysis

Economic analysis will be carried out by our health economist.

Both within trial and lifetime cost-effectiveness analysis will be performed. In within trial analysis, costs will be estimated by applying national unit costs to items of resource use (monitoring, hospitalisation, treatment, health, and social care) to estimate the mean cost per participant in each arm of the trial. Cost-effectiveness will then be estimated as the incremental cost per syncope episode avoided and the incremental cost per quality-adjusted life year (QALY) gained, with QALYs being estimated from EQ5D questionnaires.

Lifetime cost-effectiveness will be estimated using decision analytic modelling from published sources of life expectancy, annual costs and corresponding annual utilities. This will explore the potential impact of events, such as syncope episode resulting in death or injury, that have consequences beyond the timeframe of the trial.

9.2.4 Interim analysis

In addition to the blinded sample size review to ensure that the trial achieves the required statistical power, there will be a single interim futility analysis for the primary outcome performed after the 18th month of recruitment (end of study month 25). At this point 6 months of 1 year follow-up data will be available. Should for any reason less than 2234 participants have been recruited up to end of the 18th month of recruitment, then this single interim futility analysis will guide whether if a study time extension should be considered. We anticipate that at least 400 participants will have undergone 12 months follow-up for the primary outcome at this point and will be able to be analysed in this futility analysis.

Details of the futility analysis will be pre-specified as part of the statistical analysis plan for the trial. The futility analysis will be performed by an unblinded ECTU statistician. Briefly, the conditional power of the trial will be calculated based on the treatment effect observed up to the current point in the trial and assuming that this effect will also be present during the remaining period of recruitment and follow-up.

The independent Data Monitoring Committee (DMC) will review the results of the futility analysis: a conditional power of 20% or less will be used as a prompt for a discussion about whether the trial should be stopped for futility. This futility analysis will be non-binding and the DMC will therefore have the scope to consider, for example, possible benefits of the intervention

on secondary outcomes, any potential time lag in the emergence of a treatment effect and other data external to the trial before arriving at its final recommendation over whether to stop the trial for futility.

10 ADVERSE EVENTS

A secondary endpoint for the study is serious outcomes at 90-days, 1 and 2 years. 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 initial ambulatory ECG recording both in the intervention and standard care groups. Participants will be asked through the automated monthly email/text questionnaire at month 2, whether they suffered any complications related to wearing any monitoring devices in the first 2 months of the trial.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will 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 frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11.2.1 Internal recruitment pilot

This study will include an internal recruitment pilot phase with stop-go recruitment milestone criteria to mitigate risk to the funder. This internal pilot will be used to confirm recruitment rates and aims to recruit the first 400 participants (almost one fifth of the sample size) from 10 sites by the end of study month 13.

We will attempt initially to open high recruiting sites from our previous experience of IPED, RAPID-CTCA and TARGET-CTCA. We have ‘front loaded’ the clinical trial unit resource to achieve these targets and will undertake most preparatory and approvals work before the official grant start date. The pilot will take place in 10 sites chosen to reflect those centres that will take part in the main trial.

For a stop-go guideline we will use a Green-Amber-Red approach.

- Green = if all green criteria achieved then continue unchanged
- Amber = if any amber criteria present (but no red criteria present) then make changes, including opening more sites.
- Red = if any red criteria present then the study will be stopped unless rectifiable causes can be identified. This decision will be made by the independent TSC.

By the end of study month 13, the aim is to have 400 participants (18%) enrolled with an average recruitment rate/site/month of at least 5 participants in the best 60% of sites, with at least 10 sites open. ALL the criteria need to be met to achieve a Green assessment. Site recruitment rates will be calculated from each site's opening date.

Should by the end of study month 13, overall recruitment be less than 400 participants, OR average recruitment rate/site/month is less than 5 participants in the best 60% of sites, OR there are less than 10 sites open, then an 'Amber' assessment will lead to expanding the number of NHS sites recruiting. Because of the per participant fee strategy, the study is not reliant on sites recruiting research staff and are focussing on sites with existing infrastructure. Opening further sites will therefore not increase costs and will reward high recruiting centres.

Should by the end of study month 13, ANY 'red' study progression criteria are met then we may consider the study unfeasible, and the study may be stopped unless rectifiable causes can be identified. This decision will be made by the independent TSC and funder (who will have representation on the TSC).

Table 5: Internal recruitment pilot study progression criteria

By end of study month 13	Red	Amber	Green
Total number of participants recruited	≤200	201-399	≥400
% recruitment of total required	9%	10-17%	18%
Average recruitment rate/site/active months in the best 60% of sites *	3	4	5
Number of sites open	<5	5-10	>10

* Sites recruitment rate will be calculated from site opening date.

Further 12 month assessment

If by the end of study month 19, overall recruitment is less than 1300 participants (58%), OR average recruitment rate/site/month is less than 6 participants in the best 60% of sites, OR there are less than 20 sites recruiting, we will further expand the number of NHS sites recruiting. We will also consider whether study extension is required.

If by the end of study month 19, overall recruitment is less than 600 participants (27%), OR average recruitment rate/site/month is less than 4 participants in the best 60% of sites, OR there are less than 10 sites recruiting, then we may consider the study unfeasible, and the study may be stopped unless rectifiable causes can be identified. This decision will be made by the independent TSC.

11.2.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The details of the TSC will be captured in a separate charter.

11.2.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The details of the DMC will be captured in a separate charter.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained, and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The 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 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 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).

Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) 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 Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

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

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

12.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 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 Investigator 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 information, which is confidential or identifiable, and has been 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.

12.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) about the collection, storage, processing, and disclosure of personal information.

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

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place

STUDY CONDUCT RESPONSIBILITIES

12.3 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 will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e., protocol waivers, will not be approved by the sponsors 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 3 days of becoming aware of the violation. All protocol deviation logs, and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 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. Participants will be asked if they agree for identifiable data to be stored by their local study team for up to 15 years in order that it may be used for future ethically approved studies. All participants can opt out of this without affecting their trial participation.

12.7 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) 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, and R+D Office(s) and co-sponsors 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. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

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

12.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

The Intervention will not continue to be provided following the end of the study as participants will have completed the full 14-day investigation.

12.9 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the UK's NHS will have the benefit of NHS Indemnity.
- Sites out with the UK will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

The Trial Management Group will write a publication policy early in the course of the study.

We will disseminate the results of this study widely through high impact peer-reviewed publications, presentations at international conferences, local and national websites, charity newsletters and websites and media outlets such as television and radio.

We will also share our results through specific interest groups such as Arrhythmia alliance.

We will also disseminate findings amongst guideline development groups such as ESC, SIGN, NICE and American College of Cardiology (ACC), all of whom we have established links with.

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