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

Statistical Analysis Plan

CONFIDENTIAL

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List of Abbreviations

Abbreviation	Full name
ACS	Acute coronary syndrome
AF	Atrial flutter
AMI	Acute myocardial infarction
BNP	B-type natriuretic peptide
CCU	Cardiac care unit
CI	Confidence interval
CP	Conditional power
CRF	Case report form
CSRS	Canadian syncope risk score
CVA	Cerebrovascular accident
DMC	Data monitoring committee
ECG	Electrocardiogram
ECTU	Edinburgh Clinical Trials Unit
ED	Emergency department
GI	Gastrointestinal
GOF	Goodness of fit
GTN	Glyceryl trinitrate
HDU	High dependency unit
ICU	Intensive care unit
IQR	Interquartile range
ITT	Intention to treat
LRTI	Lower respiratory tract infection
MAR	Missing at random
MCAR	Missing completely at random
SAH	Subarachnoid haemorrhage
SD	Standard deviation
SDEC	Same day emergency care
TIA	Transient ischemic attack
TSC	Trial steering committee
UTI	Urinary tract infection
SVT	Supraventricular Tachycardia
VT	Ventricular Tachycardia

1. INTRODUCTION

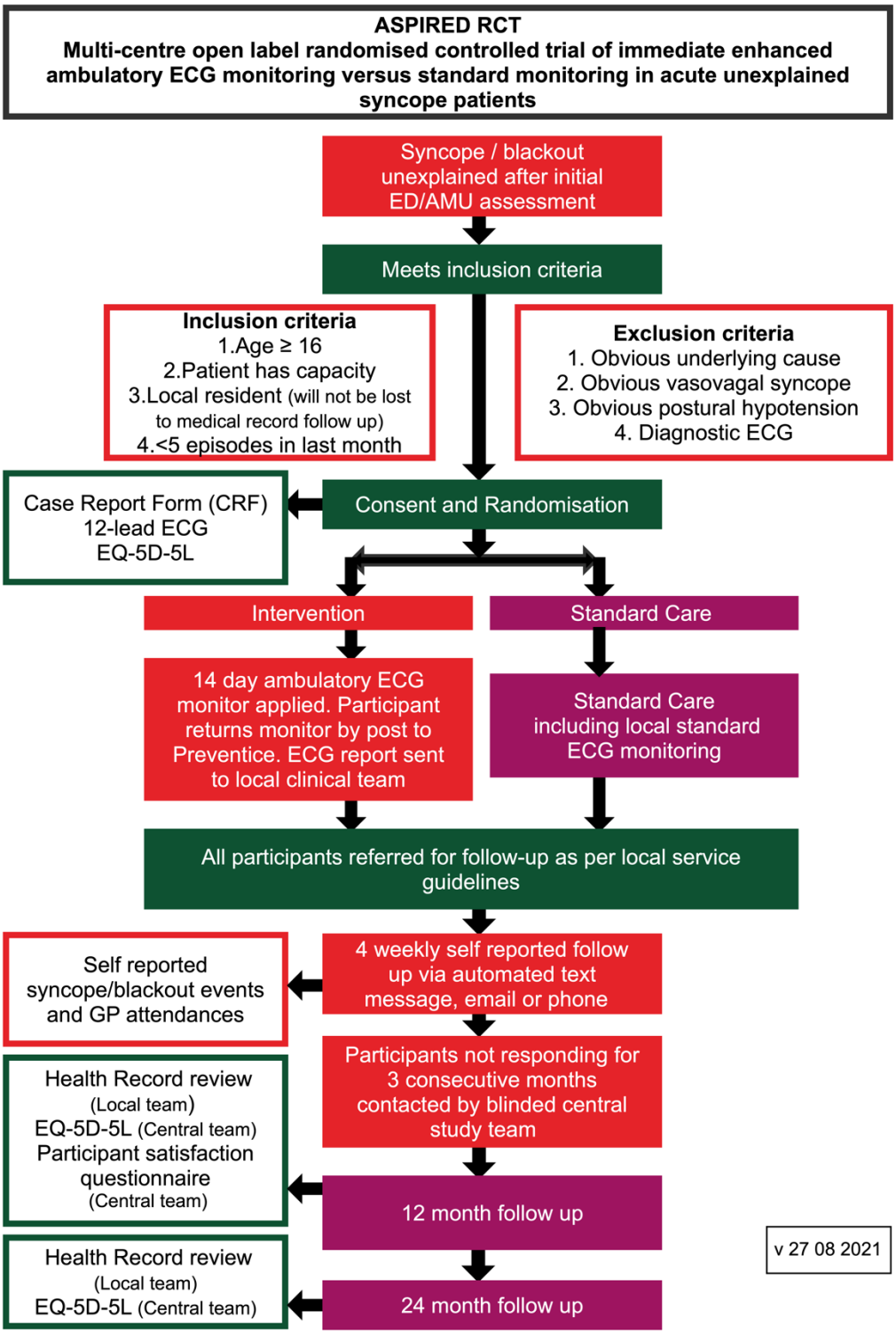
P: Population	Adults presenting acutely to UK hospitals with syncope remaining unexplained after initial ED/AMU assessment
I: Intervention	14-day ambulatory heart monitor placed on patients
C: Comparator	Standard care monitoring
O: Primary Outcome	Number of self-reported episodes of syncope at one year

- 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. An ECTU database programmer will create the allocation sequence 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 18 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.

The analysis plan covers the formal interim analysis as well as the end of trial analysis. Furthermore, the statistical analysis plan does not cover the health economics analysis which will be addressed in a separate health economic analysis plan.
This document has been prepared based on the ECTU standard operating procedure, ECTU_SOP_ST_04 Statistical Analysis Plans v6.0. Moreover, the details of this statistical analysis plan is based on the ASPIRED study protocol version 3.0, dated 14 March, 2022.

Schematic diagram of the study design (Figure 1)



2. Statistical methods section from the protocol

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.

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.

2.3 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. 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.

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.

3 Analysis population

All randomised patients will be analysed based on their allocated intervention group. Wherever possible, we will include all randomised patients regardless of compliance to the intervention, in accordance with the intention to treat (ITT) principle. This approach will be applied both to efficacy and safety analyses.

4. Overall Statistical Principles

Our primary analysis will be ITT analysis. Descriptive analysis will be conducted to present the explanatory variables split by the two study arms (intervention and standard care). We will present dichotomous and categorical variables as counts (percentages) in each category. Furthermore, we will present counts and continuous variables as mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum. We will examine the normality of the continuous variables visually by constructing histograms and quantile-quantile (Q-Q) plots.

All performed statistical tests will be two-sided with a significance level of 5%. Moreover, the two-sided 95% confidence interval (CI) will be presented unless otherwise stated. Proportion of missing data will be reported for all variables. If there is a high (greater than 5%) proportion of missing data on outcome measures, we will consider conducting multiple imputations assuming the mechanism of missingness is missing at random (MAR) or missing completely at random (MCAR).

The SAS statistical package will be used for this analysis.

4.2 Multiplicity

There will be no adjustment for multiple testing in any of the conducted analyses because they address the pre-specified objectives and there is only one primary outcome. Secondary outcomes are for explanatory purposes and they are pre-specified. Furthermore, the number of performed analyses will be clearly recorded in any publications resulting from this trial.

5 List of Analyses

The date of first and last patient randomised, the number of participants screened, eligible, randomised, receiving intervention and followed up will be reported to enable a CONSORT flow chart to be populated. This will present the number (%) of participants, split by intervention group.

5.1 Baseline Characteristics

We will summarise the following baseline data by intervention group and overall. Type of consent and demographic data are assessed at baseline (pre-randomisation); the other measures are recorded at baseline (post-randomisation). Where a given data item is assessed on more than one occasion, we report the first recorded item in this section. We will not perform any formal statistical testing.

Type of consent [In person/remote]

Demographic data

- Age at randomisation (years)
- Sex [Male/Female]
- Ethnicity [White/Asian/Black/Mixed/Other]

Past medical history

- Previous episodes of syncope prior to this attendance [Yes/No]
- >1 episode in the last year? [Yes/No]
- Coronary artery disease [Yes/No]
- Myocardial Infarction [Yes/No]
- Atrial Fibrillation/Flutter [Yes/No]
- Congestive Cardiac Failure [Yes/No]
- Valvular Heart disease [Yes/No]

- Hypertension [Yes/No]
- Diabetes [Yes/No]
- Epilepsy [Yes/No]
- Chronic lung disease [Yes/No]
- Chronic kidney disease [Yes/No]
- Pacemaker or implantable defibrillator [Yes/No]
- Rockwood clinical frailty score [1-9]

COVID-19 Details

- Has the participant reported receiving any COVID-19 vaccine? [Yes/No]
- Has the participant reported ever receiving a positive COVID-19 diagnosis? [Yes/No]

History of syncope episodes

- Prodromal/preceding symptoms [Yes/No]
- Palpitation prior to syncope [Yes/No]
- Associated chest pain [Yes/No]
- Subjective shortness of breath [Yes/No]
- Associated headache [Yes/No]
- Situational symptoms, i.e. micturition [Yes/No]
- Related to glyceril trinitrate (GTN) use [Yes/No]
- Related to exertion [Yes/No]
- Witnessed seizure activity [Yes/No]

ED observations

- Blood pressure (mmHg)
- Postural Drop [Yes/No/Not available]
- Systolic difference if performed (mmHg)
- Pulse (bpm)
- Oxygen saturation on room air [Yes/No/Not available]
- Bradycardia<= 50 in ED or pre-hospital [Yes/No/Not available]
- Respiratory rate (breaths per minute)

ED examination

- Heart murmur heard [Yes/No/Not available]
- Clinical signs of heart failure present? [Yes/No/Not available]

- New neurological signs on examination? [Yes/No/Not available]
- Faecal occult blood/melena on PR? [Yes/No/Not available]

Admission ECG

- Rate (bpm)
- QRS Axis ()
- QTc (ms)
- QRS duration/ms (ms)
- Sinus rhythm [Yes/No]
- Any Q wave (not in lead 3)? [Yes/No]
- PR> 200 msecs? [Yes/No]

ROSE rule (POSITIVE IF ANY ANSWERED YES, ELSE NEGATIVE (1))

- Associated chest pain
- Saturation ≤94% on admission on room air
- Bradycardia ≤50 in ED or pre-hospital?
- Faecal Occult Blood/Melena on PR?
- Any Q wave (not in lead 3)
- Haemoglobin ≤90 g/l
- BNP > or equal to 300 pg/ml

Canadian Syncope Risk Score (CSRS) at randomisation (minus 3 to +11) (2)

- Prodromal/preceding symptoms OR Situational symptoms i.e. micturition? No = 0, YES = minus 1)
- Heart disease history (IHD, CAD, MI, AF, CHF, valvular disease) (No = 0, YES = +1)
- Systolic (ie first reading) Blood Pressure <90 or >180 mmHg (No = 0, YES = +2)
- Troponin >99th percentile of normal population? (No = 0, YES = +2)
- QRS axis (Abnormal QRS axis <-30° or >100° = +1, else 0)
- QRS duration/ms (If QRS duration >130 ms = +1, else 0)
- QTc (Corrected QT interval >480 ms = +2, else 0)
- ED diagnosis: How likely do you think that the patient has an underlying cardiac cause of syncope (0-10) if 7 or greater (+2); if <7 =0

Clinical blood results

- Haemoglobin (g/L)
- Haematocrit ratio (%,L/L)
- Troponin > 99th percentile of normal population? [Yes/No/Not available]
- BNP recorded [BNP/NT pro BNP/Not available]
- BNP (pg/ml)
- NT pro BNP (pg/ml)

Management from ED/ Acute Medicine unit

- Disposition [Discharged home/Admitted to Observation/clinical decision unit/SDEC unit/Admitted to medicine (non-monitored)/Admitted to medicine (monitored)/Admitted to cardiology/CCU (monitored)/Admitted to care of the elderly/ Gerontology/Admitted to ICU (Intensive Care)/Admitted to HDU (High Dependency)/Other
- Planned outpatient follow up? [Yes/No]
- In those admitted, reason(s) for admission [High risk syncope/for cardiac monitoring/Comorbidity/Syncope investigation/Social/Other/Not known]
- How likely does treating ED clinician think that the patient has an underlying cardiac cause of syncope? [1 (Least likely) / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10 (Most likely) / Not known]

Index hospital admission: discharge details

- Duration of index hospital stay (days)
- Was the participant discharged alive? [Yes/No]
- Did participant suffer any problems related to wearing any ECG monitoring devices during index admission? [Yes/No]
- Hospital Discharge Diagnosis? [(Acute CVA / subdural / SAH / TIA)/(Alcohol related/ alcohol related seizure)/(Allergic reaction / anaphylaxis/AMI /ACS)/Anaemia/(Anxiety / psychogenic / hyperventilation)/Aortic stenosis/Benign positional vertigo/(Cardiac arrhythmia: Atrial flutter / AF)/(Cardiac arrhythmia: Heart block / Bradycardia / Sick Sinus)/Cardiac arrhythmia: Ventricular arrhythmia/Carotid sinus sensitivity/Dehydration/GI bleed/GTN syncope/Heart failure/Hypertrophic cardiomyopathy/(Hypoglycaemia/Infection / sepsis / LRTI / UTI)/Malignancy/Neurological seizure/Postural hypotension secondary to

dehydration/Postural hypotension secondary to medication/Postural hypotension other cause/Pulmonary emboli/Situation syncope (cough / sneeze / defaecation)/ Unexplained syncope/(Vasovagal / neutrally mediated / reflex)/ Viral illness/Other/Not available]

5.2 Outcomes

5.2.1 14-Day ECG Patch Result (Intervention group only)

- Result obtained? [Yes/ No]
- Result actioned (passed to treating clinician) [Yes/ No]
- Device Wear Time (days, hours, minutes)
- Device Analysable Time (days, hours, minutes)
- Maximum Heart Rate (bpm)
- Minimum Heart Rate (bpm)
- Average Heart Rate (bpm)
- Premature Ventricular Complexes [< 1%/>= 1%]
- Premature Supraventricular Complexes [< 1%/>= 1%]
- Number of triggered events
- %AF burden [< 1%/>= 1%]
- AF - number of episode
- Longest AF episode [< 1 minute/>= 1minute]
- SVT - Total number of episodes
- Fastest SVT episode (bpm)
- Longest SVT episode (beats)
- AV block - number of episodes
- Type of block present
- Number of pauses
- Longest pause (seconds)
- Number of VT episodes
- Longest VT episode (bpm)
- Fastest VT episode (beats)

5.2.2 90 Days data points

- Did participant have follow-up clinic appointment? [Yes/No]
- Did participant attend follow-up clinic? [Yes/No]
- TYPE OF FOLLOW-UP CLINIC ATTENDED (Specialist Syncope clinic; General/Acute Medicine; Care of the Elderly / Gerontology clinic; Cardiology clinic; Ambulatory ED clinic; Emergency Medicine; Ambulatory Care; Neurology)
- Number of episodes of syncope resulting in an attendance to hospital in the first 90 days from hospital admission identified in the medical records

5.2.3 Clinically significant cardiac dysrhythmia and Diagnostic ECG/symptom correlation

These outcomes will include aggregate data from 90 days, 1 year, 2 year forms

- Clinically significant cardiac dysrhythmia captured [YES/NO]
- If so, what (can tick >1): Ventricular Fibrillation (VF); Ventricular Tachycardia (VT) ≥120 beats per minute (bpm) for ≥30 seconds; Ventricular Tachycardia (VT) ≥120 bpm 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; Supraventricular tachycardia >100 beats per minute ≥30 seconds; Atrial flutter/fibrillation with ventricular rate >100 bpm or <60 bpm ≥30 seconds; New Atrial flutter/fibrillation ≥30 seconds
- Was the captured dysrhythmia symptomatic [YES/NO]
- If Diagnostic ECG/symptom correlation obtained and not rhythm above then what was diagnostic ECG [Sinus rhythm/ectopics/sinus tachycardia; Other]
- How was dysrhythmia detected? [Wired inpatient Monitoring; 24 hour tape (Holter); 48 hour tape; 72 hour tape; 5 day tape; PREVENTICE 14 day ECG

monitor (part of trial); 7 day patch monitor; 14 day patch monitor; Mobile Cardiovascular Telemetry (MCT) ; Implantable Loop Recorder]

5.2 Blinded sample size review

We will provide interim data summaries, as outlined in the DMC charter, for data monitoring committee (DMC) meetings. Furthermore, we will perform a blinded sample size review after 50% of participants have been randomised, which will be considered by the Trial Steering Committee (TSC).

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 over-dispersion). 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. We will use the formula number 2 in the published paper "Blinded Sample Size Re-estimation with Negative Binomial Count in Superiority and Non-inferiority Trials" that can be found in ':\ECTU Current Trials\1 CURRENT PROJECTS\ASPIRED\TMF\9 CRF_STATS_DM\4 STATS\Sample size\Sample size reassessment\'. (1) 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 demonstrate that such an approach does not inflate the type I error and ensures that the study attains its planned statistical power (3). On average, a small increase in sample size is required to achieve this.

5.3 Interim Analyses

At the end of the 18th month of recruitment, an interim futility analysis of the primary outcome will be reviewed by the DMC. If the number of participants randomised is less than 2234 by the 18th month, this interim analysis will help guide the decision whether an extension of the study period is needed.

We will calculate the conditional power (CP) depending on the data available at the time of the interim data cut. The calculation will be based on the same assumptions as in the original sample size calculation (protocol section 9.1.2), except that we will used the observed overdispersion parameter in place of the previously assumed value of 0.25; and we will assume that the treatment effect of the intervention to the date of the interim analysis will continue for the remaining participants and follow-up because the interim analysis is taking place very late in the trial. If CP is 20% or less (the probability that the final analysis is statistically significant is less than or equal to 20%), this will prompt a discussion about whether the trial should be stopped for futility.

5.4 Primary outcome Number of self-reported episodes of syncope at one year.

Self-reported syncope episodes up to and including the events reported nearest to the one year time point (whether before or after) will be included in the analysis of the primary outcome. We will construct a negative binomial model. The response variable will be the number of self-reported episodes of syncope at one year. Centre will be included as a random effect in the final model, intervention group as a fixed effect. An offset term for follow-up duration will be included to account for participants with partial follow up. The incidence rate ratio (intervention:standard care) of self-reported episodes of syncope with the corresponding 95% CI and P-value will be reported. We will use the Pearson Chi-squared statistic to test goodness of fit (GOF) of the model. A sensitivity analysis will evaluate the impact of the potential competing risk of death by considering a death to represent a syncope event rather than a censoring event.

5.4.1 Subgroup analysis of primary outcome

A subgroup analysis according to syncope risk at baseline will be performed. The following subgroups of the CSRS at randomisation will be considered:

- Low risk (CSRS -3 to 0)
- Medium risk (CSRS 1 to 3)
- High risk (CSRS 4 to 11)

We will fit the same model as used in the analysis of the primary outcome (Section 5.4) with the addition of fixed effects for CSRS subgroup and the intervention by CSRS subgroup interaction term. We will report the incidence rate ratio (intervention:standard care) and its 95% CI within each subgroup and the p-value for the interaction term.

5.5 Secondary outcomes

5.5.1 Binary secondary outcomes

1. Clinically significant cardiac dysrhythmia (Serious and/or symptomatic cardiac dysrhythmia Table 1) at (a) 90-days, (b) 1 year and (c) 2 years.
2. (a) 30 day, (b) 1 year and (c) 2 year all cause death.
3. Detection of diagnostic ECG/symptom correlation (symptomatic) at (a) 90-days, (b) 1 year and (c) 2 years.

For binary outcomes, we will construct a multivariable logistic regression model which includes intervention group and centre. To allow for clustering on sites, we will use mixed effects logistic regression model by including the centres as a random effect and intervention group as a fixed effect. In the event that the random effect is not appropriate (the model does not converge), we will consider including centre as fixed effect. We will report the odds ratio (intervention:standard care) and 95% CI.

5.5.2 Count secondary outcomes

1. Number of self-reported episodes of syncope (count variable) 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. We will analyse these outcomes in the same way as the primary outcome. Outcomes (a) and (b) will be measured using the self-reported outcomes reported up to and including the record nearest to the relevant time point (whether before or after).
2. Index presentation hospital admission rate (number of admissions) will be analysed using the negative binomial model in the same way as for the primary outcome.

3. Number and type of diagnostic tests and therapeutic interventions (count variables) at (a) 1 year and (b) 2 years. They will be analysed using the negative binomial model in the same way as for the primary outcome.

5.5.3 Continuous secondary outcomes

1. Duration of index hospital stay
2. In the intervention group, duration of enhanced ambulatory ECG monitoring required to detect clinically significant cardiac dysrhythmia.

Continuous secondary outcome 1 will be summarised by intervention arm, continuous secondary outcome 2 will be summarised overall.

The effect of the intervention on continuous secondary outcome 1 will be examined using a normal linear mixed model. The study site will be included as a random effect. An indicator variable for randomised intervention group allocation will be included as a fixed effect. We will report the adjusted mean difference between groups (intervention minus standard care) with its 95% confidence interval and P-value.

For continuous secondary outcome 2 we will use a normal linear mixed model including site as a random effect. We will report the adjusted mean along with its 95% confidence interval.

5.5.4 Time-to-event outcome

Time to detect clinically significant cardiac dysrhythmia (i.e. time to clinician being aware).

5.5.4.1 Univariable analysis

Analysis of event proportions over time will be presented using Kaplan-Meier survival curves by randomised group.

5.5.4.2 Proportional hazards modelling

The proportional hazards assumption for the intervention effect will be examined. Background data from the ROSE study (4, 5) indicate that deaths will be uncommon in this patient population (2.7% at 90 days) and so participants who die or are lost to follow up will be considered censored in this analysis. A sensitivity analysis will evaluate this assumption by considering deaths as outcome events rather than censoring events.

If the proportional hazards assumption is not violated, we will assess the impact of the intervention using a Cox proportional hazards model including a term for the intervention arm. Furthermore, we will include the study centre as a random effect (frailty term). If the random effect causes model fitting problems, we will consider other methods such as including study centre as a fixed effect. The adjusted hazard ratio for intervention:standard care with its 95% confidence interval and P-value will be reported.

We will assess the proportional hazards assumption graphically and if the assumption is violated, we will compare the treatment arms using a restricted mean survival time approach.

5.5.5 Satisfaction questionnaire analysis

Patient Satisfaction (measured using a patient questionnaire) at 1 year. Each of the six questions will provide a categorical ordinal variable ranging from 1 to 5, corresponding to “strongly disagree”, “disagree”, “neutral”, “agree”, “strongly agree”. The results for each question will be summarised by intervention group and analysed using a generalised linear mixed model (proportional odds logistic regression). The study centre will be included as a random effect, intervention group as a fixed effect. For each question, the intervention effect will be reported as a common odds ratio (intervention:standard care) with its 95% confidence interval and P-value.

5.5.6 Subgroup analysis of secondary outcomes

The subgroup analysis by CSRS outlined in Section 5.4.1 will also be applied to selected secondary outcomes:

- Clinically significant cardiac dysrhythmia at 90 days; at 1 year; at 2 years (see Section 5.5.1)
- Number of diagnostic tests and therapeutic interventions at 1 year; at 2 years (see Section 5.5.2)

To perform the subgroup analysis, we will fit the same model as described in the relevant section for each secondary outcome, with the addition of fixed effects for CSRS subgroup and the intervention by CSRS subgroup interaction term. We will report the intervention effect parameter and 95% confidence interval within each subgroup and the p-value for the interaction term.

5.8 Safety

Adverse events related to the intervention, serious adverse events, and suspected unexpected serious adverse reactions will be summarised by intervention group. We will report the number of events and the number of participants who experienced at least one event. We will include participants according to randomised group as this intention to treat approach is the preferred method(6). In a supporting analysis we will stratify the events in the intervention group according to whether or not the participant used the ECG patch at all.

6. Validation and QC

A second statistician will do the following to validate the main statistician's work

1. Independently programming the primary outcome analysis, including deriving the outcome, and checking the results and conclusions of the primary outcome analysis.
2. Reading the statistical report to ensure it is correct and understandable by clinicians.

7. Data sharing

A file, or set of files, containing the de-identified individual participant data corresponding to the final statistical analysis data set will be prepared. This will be made available, alongside a package including the data dictionary, trial protocol, statistical analysis plan and other meta-data, with access controlled according to the ECTU standard operating procedure ECTU_OP_15: Data Access Request and Application Management.

8. References

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6. Yang F, Wittes J, Pitt B. Beware of on-treatment safety analyses. Clinical trials (London, England). 2019;16(1):63-70.

Appendix 1 ROSE rule and CSRS scoring

ROSE rule If data for a ROSE rule item is missing, we will score that item as zero. If three or more items are missing, we will not calculate the ROSE rule for that participant.

CSRS In line with the published validation of CSRS, if data is missing for one item, that item will be scored as zero. If three or more items are missing for a participant, we will not calculate a CSRS score for them.

ASPIRED_SAP_V1.0

Final Audit Report 2022-12-08

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Status:	Signed
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