accord
Academic and Clinical Central Office for Research and Development

NHS Lothian

British Heart Foundation

aspired

The ASPIRED Study Information for sites

What is syncope?

Lay term: Blackout

Transient loss of consciousness (TLoC) with inability to maintain postural tone and immediate complete spontaneous recovery without medical intervention

Video courtesy of Dysautonomia Information Network (www.dinet.org)

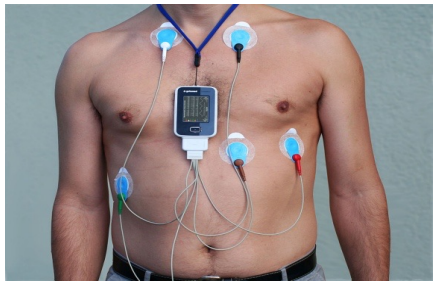
Rationale for Trial

- Syncope is common
  - 650,000 patients present to UK ED/AMU per year
- Diagnosis is difficult
  - patients recovered, normal exam/ECG
- Three common categories of underlying
  - Reflex (vagal), Postural, Cardiac (Dysrhythmia/Structural)
- 10% will have an underlying serious cardiovascular problem, majority are Dysrhythmic
- Need symptom rhythm correlation

Rationale for Trial (continued)

Traditional symptom rhythm correlation methods

- Holter monitor
  - rarely picks up abnormal heart rhythm



- Event recorders
  - can monitor over longer periods but must be activated

- Implantable Loop recorders (ILR)
  - expensive, require a surgical procedure, reserved for patients who remain unexplained, commonly not deployed for many months after the index event

Rationale for Trial (continued)

- There is evidence that pick up of the underlying dysrhythmia is highest when a device is applied early, ideally at the index visit **[1-3]**
- Prolonged external ambulatory ECG monitoring (14 days) novel
- Suitable for ED/AMU use but utility still undefined
- Hypothesis
  - Applying prolonged cardiac monitoring early after syncope at the index visit is the optimum strategy to detect, diagnose, treat and exclude underlying cardiac dysrhythmia.
- The ASPIRED study
  - Multi-centre open label randomised controlled trial of immediate enhanced ambulatory ECG monitoring versus standard monitoring in acute unexplained syncope patients:

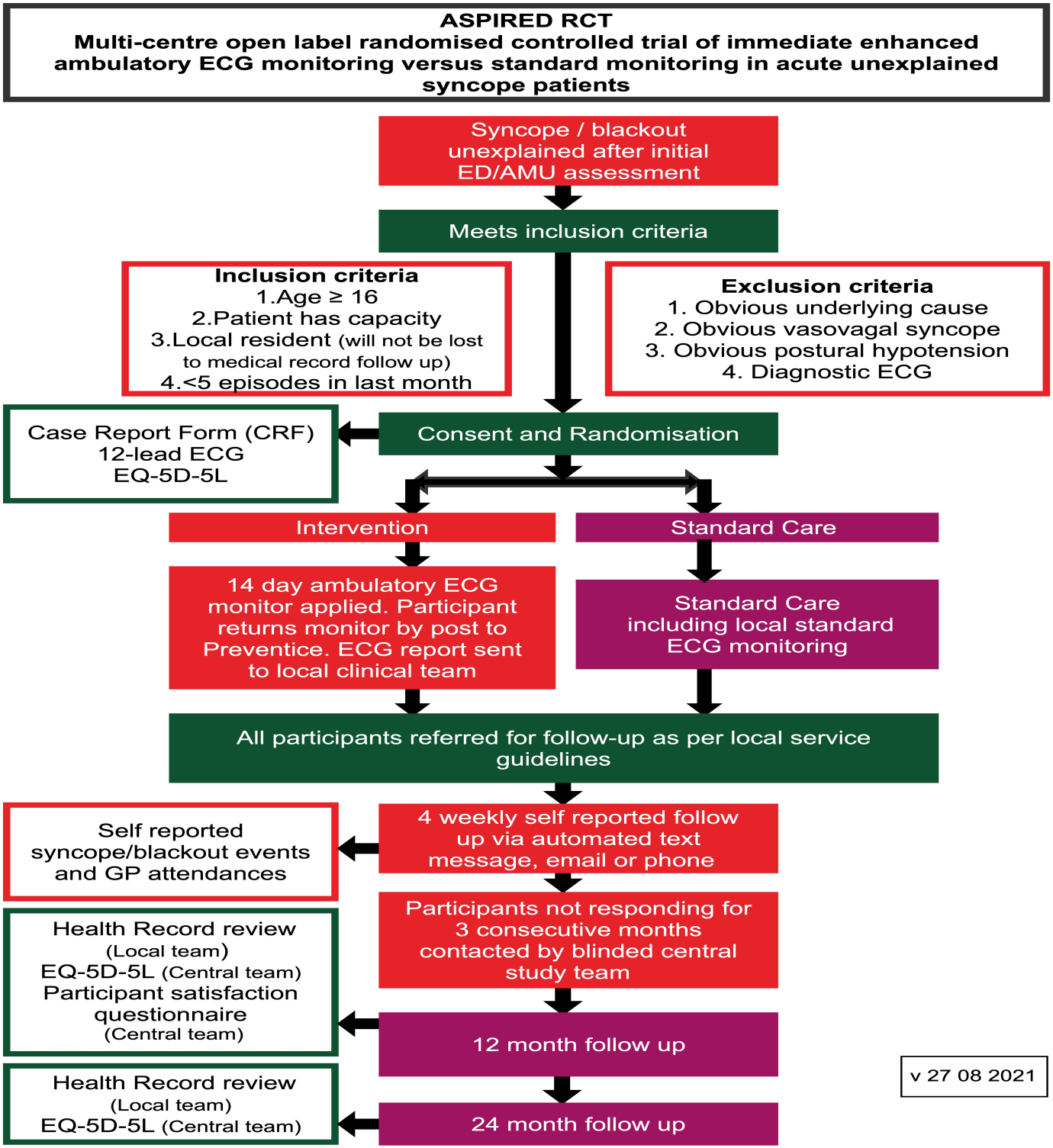
[1] Reed MJ et al. The PATCH-ED study. *Emerg Med J* 2018; 35:477–485 **[2]** Locati ET et al. SYNARR-Flash study. Europace 2016; 18: 1265–1272
[3] Thiruganasambandamoorthy et al. Circulation 2019; 139: 1396–1406

Trial Overview

- Prospective, parallel group RCT; Phase III; Non-CTIMP
- 2234 Patients across 20-30 UK sites

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 during or shortly after ED/AMU assessment
C: Comparator	Standard care monitoring
O: Primary Outcome	Number of episodes of syncope at one year including both those identified in the medical records and self-reported episodes

- Collaborators – EMERGE/ Edinburgh CTU / University of Sheffield


ASPIRED RCT
Multi-centre open label randomised controlled trial of immediate enhanced ambulatory ECG monitoring versus standard monitoring in acute unexplained syncope patients
Syncope / blackout unexplained after initial ED/AMU assessment
Meets inclusion criteria
Inclusion criteria
1.Age ≥ 16
2.Patient has capacity
3.Local resident (will not be lost to medical record follow up)
4.<5 episodes in last month
Exclusion criteria
1. Obvious underlying cause
2. Obvious vasovagal syncope
3. Obvious postural hypotension
4. Diagnostic ECG
Case Report Form (CRF)
12-lead ECG
EQ-5D-5L
Consent and Randomisation
Intervention
Standard Care
14 day ambulatory ECG monitor applied. Participant returns monitor by post to Preventice. ECG report sent to local clinical team
Standard Care including local standard ECG monitoring
All participants referred for follow-up as per local service guidelines
Self reported syncope/blackout events and GP attendances
4 weekly self reported follow up via automated text message, email or phone
Participants not responding for 3 consecutive months contacted by blinded central study team
Health Record review
(Local team)
EQ-5D-5L (Central team)
Participant satisfaction questionnaire
(Central team)
12 month follow up
Health Record review
(Local team)
EQ-5D-5L (Central team)
24 month follow up
v 27 08 2021

Inclusion criteria

- Syncope remains unexplained after initial ED/AMU assessment
  - No ‘obvious’ underlying cause *
- Aged ≥ 16 years
- Patient has capacity
- Local resident
  - (resides within local health board area and local team able to follow-up)
- <5 episodes of syncope in the previous month

Exclusion criteria

- Obvious underlying cause after assessment
  - **Vasovagal:** Features **(see Table) AND** absence of structural heart disease **AND** normal physical examination **AND** normal ECG

Prolonged pre-syncope associated with 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

  - **Dysrhythmia** on pre-hospital or hospital ECG as likely cause of syncope
  - **Postural hypotension** (symptomatic postural drop >20 mmHg **AND** suggestive history)
  - Confirmed diagnosis of Pulmonary Embolus or Acute Myocardial Infarction
  - Radiological diagnosis or clinical signs/symptoms of CVA/TIA or SAH
  - Evidence of haemorrhage, alcohol or illicit drugs, epileptic seizure, hypoglycemia, head trauma, **Other** obvious cause of syncope as presumptive cause of TLoC

Exclusion criteria

Inability to consent	Previous recruitment into the study	Patient in custody or prison
Aged <16 years	Patient normally resides outwith health board area	5 or more episodes of syncope in previous 4 weeks

Trial Objectives

Primary

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

Trial Objectives

Secondary

- To determine whether immediate, enhanced (14-day) ambulatory ECG monitoring in acute unexplained syncope patients can:
- Decrease the time to detection of clinically significant cardiac dysrhythmia compared to standard care monitoring.
- Increase the rate of detection of clinically significant cardiac dysrhythmia at 90 days and 1 year compared to standard care monitoring.
- Increase the rate of ECG/symptom correlation at 90 days and 1 year compared to standard care monitoring.
- Demonstrate cost effectiveness compared to standard care monitoring.
- Decrease the number of episodes of syncope (composite of those identified in medical records and self-reported) at 90 days and 2 years compared to standard care monitoring.
- Decrease the number of episodes of syncope identified in the medical records at 90 days, 1 and 2 years compared to standard care monitoring.
- Decrease the number of episodes of self-reported syncope at 90 days, 1 and 2 years compared to standard care monitoring.
- Decrease the index hospital admission rate and duration of hospital stay compared to standard care monitoring
- Decrease 90 days, 1- and 2-year syncope recurrence rates (identified in the medical records and self-reported) compared to standard care monitoring
- Increase patient satisfaction compared to standard care monitoring
- Decrease the rate of 30 day, 1 and 2 year all cause death compared to standard care monitoring
- 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

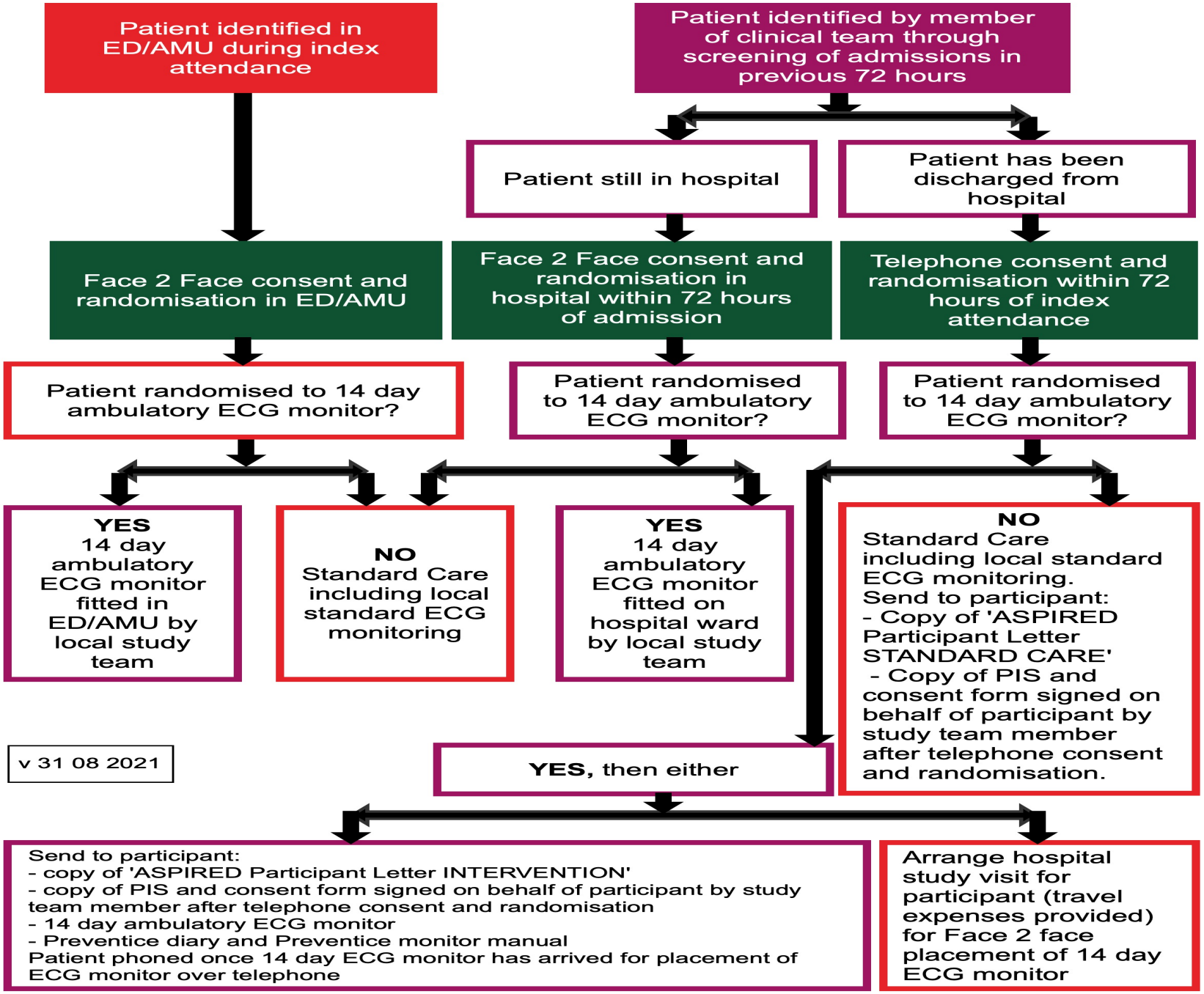
Screening

Assessment	Screening
Assessment of Eligibility Criteria	Local team ☒
Informed consent	Local team ☒
CRF completion including demographic data and contact details	Local team ☒
Routine clinical care (e.g. ECG)	Local team ☒

Screening participants

1. Recruitment from ED/AMU
2. ED/AMU patients admitted to hospital can be recruited within 72 hours of ED/AMU presentation
3. ED/AMU patients discharged can be contacted by phone and recruited within 72 hours of ED/AMU presentation
   a) Patient consented over the phone or can return to ED for consent (travel expenses included) +/- placement of 14-day ambulatory ECG (if intervention)
   b) 14-day ambulatory ECG can be also mailed (postage supplied) to the participant who can be advised over phone how to fit

ASPIRED RCT
Enrolment process



Screening participants

- Research staff participating in patient identification should be a part of the clinical team responsible for/contributing to patient's care
- Any member of the direct care/clinical team who has received trial specific training may also identify participants
- A log will be kept of patients who were approached to take part in study and subsequently found to be ineligible or not recruited

Consent & Randomisation

- Participant Information Sheet (PIS)
- 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 read out to the patient.
- The PIS will also be available on the trial website
- Patients who have provided informed consent verbally over the telephone will have a written consent form signed by the research member on the patient's behalf and this signed form will be sent to the patient with contact details of the research team should they decide to withdraw consent. The original consent form will be filed in the ISF and a copy will be filed in the participant's medical notes
- Neither participants nor treating clinicians will be blinded to allocation

Documenting participation in patient notes

- Minimum data into participant notes:

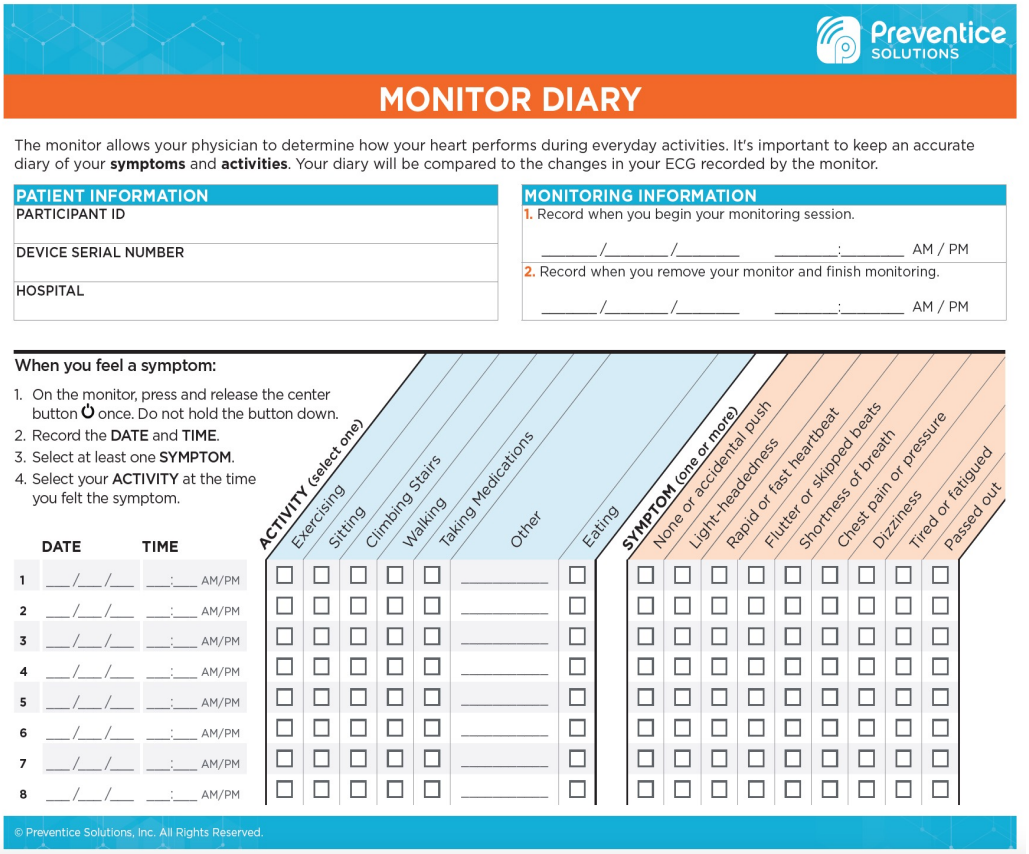
- 1. Confirm participant eligible
- 2. Brief outline of what trial involves
- 3. Detail randomisation allocation
- 4. Clearly document date of consent
- 5. Contact details for the local research team
- 6. State that participant remains in trial for 2 years
- 7. Any AEs/SAEs

- Medical record stickers may be required for participant medical notes

Participants consented by phone

- To be sent pack with:
- Covering letter
- Copy of consent form signed by research team
- PIS
- Device (if intervention arm)
- Preventice diary (if intervention)
- BG mini manual (if intervention)

(all have gone through ethics)



Preventice SOLUTIONS

MONITOR DIARY

The monitor allows your physician to determine how your heart performs during everyday activities. It's important to keep an accurate diary of your **symptoms** and **activities**. Your diary will be compared to the changes in your ECG recorded by the monitor.

PATIENT INFORMATION
PARTICIPANT ID
DEVICE SERIAL NUMBER
HOSPITAL

MONITORING INFORMATION
1. Record when you begin your monitoring session.
_____/_____/_____ _____:_____ AM / PM
2. Record when you remove your monitor and finish monitoring.
_____/_____/_____ _____:_____ AM / PM

When you feel a symptom:
1. On the monitor, press and release the center button ⏻ once. Do not hold the button down.
2. Record the **DATE** and **TIME**.
3. Select at least one **SYMPTOM**.
4. Select your **ACTIVITY** at the time you felt the symptom.

	DATE	TIME	ACTIVITY (select one)							SYMPTOM (one or more)								
			Exercising	Sitting	Climbing Stairs	Walking	Taking Medications	Other	Eating	None or accidental push	Light-headedness	Rapid or fast heartbeat	Flutter or skipped beats	Shortness of breath	Chest pain or pressure	Dizziness	Tired or fatigued	Passed out
1	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Preventice TECHNOLOGIES

BodyGuardian® MINI

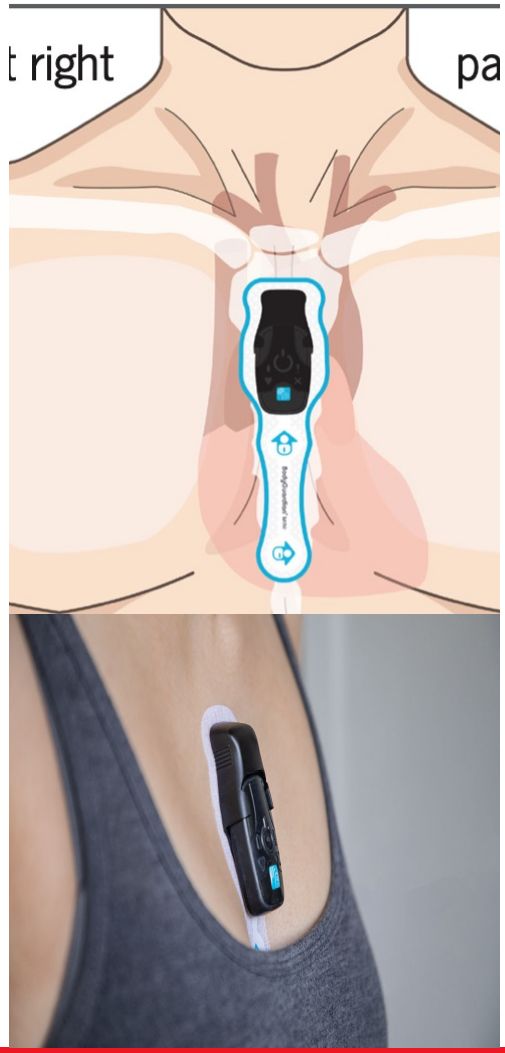
Patient Manual

Day 1

Assessment	Screening	Day 1 baseline
Randomisation	Local team	☒
Intervention group participants fitted with a 14 day ambulatory heart monitor	Local team	☒
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.	Local team	☒
EQ-5D-5L questionnaires	Local team	☒

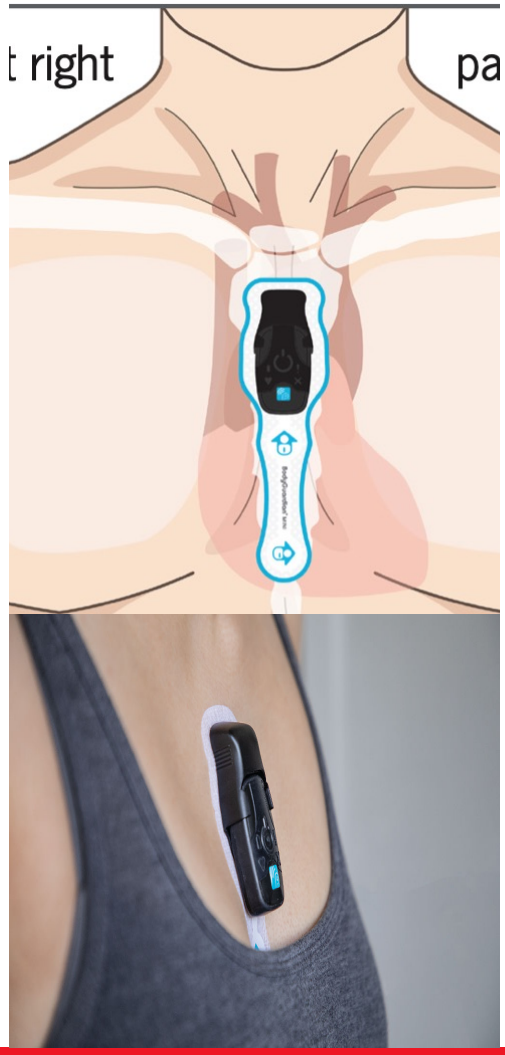
Intervention group: Applying device (see video)

- Fitted with a 14-day ambulatory ECG monitor (Preventice BodyGuardian Mini) by the study team
- 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
- The ambulatory ECG monitor will be placed on the participant's chest wall over the sternum (middle bony area of chest)
  - It is the size of a watch face, is non-invasive, water-resistant and is discrete 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
  - CANNOT BE WORN DURING MRI



Intervention group: Applying device (see video)

- The participant's skin shaved if necessary and cleaned prior to attaching the device, which is easily removed by the participant after 14 days
- The participant will wear the ambulatory ECG monitor for 14 days after which they will remove the monitor and return it in a pre-paid envelope to Preventice UK
- Any study participant with a serious dysrhythmia on the ECG report will be contacted as soon as possible by the local team and managed appropriately according to local policy
- Treatment of device findings will be at the discretion of the treating clinician at each site



Intervention group

aspired

Participant can record any symptomatic events whilst wearing the device either on the monitor dairy or by pressing and releasing the button on the monitor.

Preventice SOLUTIONS

MONITOR DIARY

The monitor allows your physician to determine how your heart performs during everyday activities. It's important to keep an accurate diary of your **symptoms** and **activities**. Your diary will be compared to the changes in your ECG recorded by the monitor.

PATIENT INFORMATION

PARTICIPANT ID

DEVICE SERIAL NUMBER

HOSPITAL

MONITORING INFORMATION

1. Record when you begin your monitoring session.
   ______/______/______ ______:______ AM / PM
2. Record when you remove your monitor and finish monitoring.
   ______/______/______ ______:______ AM / PM

When you feel a symptom:

1. On the monitor, press and release the center button ⏻ once. Do not hold the button down.
2. Record the **DATE** and **TIME**.
3. Select at least one **SYMPTOM**.
4. Select your **ACTIVITY** at the time you felt the symptom.

	DATE	TIME	ACTIVITY (select one): Exercising	Sitting	Climbing Stairs	Walking	Taking Medications	Other	Eating	SYMPTOM (one or more): None or accidental push	Light-headedness	Rapid or fast heartbeat	Flutter or skipped beats	Shortness of breath	Chest pain or pressure	Dizziness	Tired or fatigued	Passed out
1	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	______	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2	___/___/___	___:___ AM/PM	☐	☐	☐	☐	☐	______	☐	☐	☐	☐	☐	☐	☐	☐	☐	
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Standard care group

- Subsequent investigation:
  - Arranged at the discretion of the treating clinician, based on local guidance
  - NICE recommend:
    - Holter monitoring for participants who have frequent TLoC
    - Extended ambulatory monitoring with event marker for less frequent symptoms
    - Implantable loop recorder (ILR) reserved for second line investigation

Both groups

Follow up

All recruited participants regardless of allocation group should be referred for syncope assessment as per local service protocol 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

Case Report Form

- Electronic (can be printed in paper format)

- CRF
  - Some sections which require ED clinician input (e.g. Reason for admission, clinician likelihood of cardiac cause 1-10) include ‘not known’ sections

- Hard copy of ECG not required to recruit participants post ED but need to see mentioned in participants notes that it was normal and not diagnostic

Preventice Report

- Will come back on Preventice UK Database
- Each site will have a single login for this
- Report will be in pdf form and anonimsed with study number only
- Site should attach a front page to Preventice UK report with patient indentifiable information along with existing study number
- Site should send report to treating clinician – local policy should be decided as to where report should go to action (e.g. all go to syncope clinic, all to a specific clinic, all to a specific clinician, to individual treating clinician etc)

Preventice Database

Trial Database

GP letters

- The participant's GP will be informed that the participant has been enrolled in the study

- Participants GP will be informed of the results of any ECG investigations via routine hospital clinical correspondence

Arrhythmia alerts

- Site will be alerted to any serious dysrhythmia via email to be acknowledged within 1 working day, else will receive phone call
- Each site to provide working hours manned email and phone contacts
- Serious notifiable dysrhythmias:
  - VT: >100bpm >20 beats
  - 3rd degree heart block: <40 beats for ≥ 2 mins
  - SVT: >150 for ≥ 2 minutes
  - Pause: ≥6 seconds

Monthly

Assessment	Screening	Day 1 baseline	Monthly
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.			☒ Central team

Web-based questionnaire

Accessed either via text/email or phone call (participants choice)

Web-based questionnaire

- Since your last response on xx/xx/xxxx, have you experienced any further fainting or blackout episodes that have led you to lose consciousness (Y or N)?
- Since your last response on xx/xx/xxxx, how many times have you seen your GP for any reason (not just syncope - include all face to face/telephone and online consultations)
- **At month 2 ONLY, participants will be asked**
- Have you suffered any problems or complications related to wearing any ECG monitoring devices during your first 2 months of the trial?

3 monthly

Assessment	Screening	Day 1 baseline	Monthly	Every 3 months
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.			Central team	☒

Yearly

Assessment	Screening	Day 1 baseline	Monthly	Every 3 months	1 year	2 years
EQ-5D-5L questionnaires			Central team		☒	☒
NHS resource utilisation data from routine hospital electronic healthcare records extracted by the local study team)			Local team		☒	☒
Participant satisfaction questionnaire			Central team		☒	

- Local team will ask the main clinician in charge of patient's ongoing care (both arms / to include) at one year:
  - Has there been a recorded rhythm showing cause of syncope (a diagnostic finding)?
  - How was this obtained (PREVENTICE/24/48/72/5 day/ILR etc)?
  - What was the rhythm?
  - Was this a cardiac dysrhythmia (definitions)?
  - What Ix were performed?

Trial Endpoints

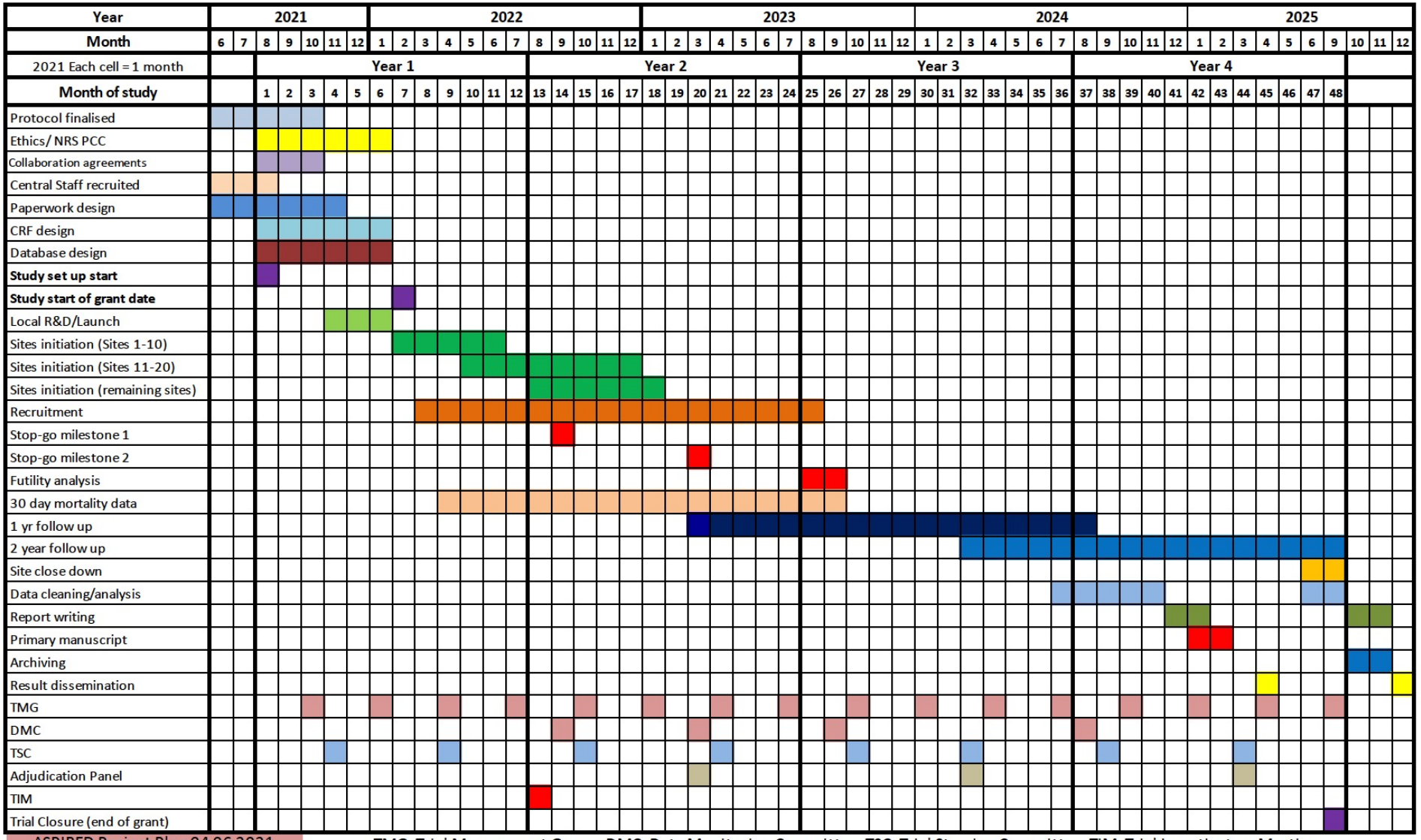
Primary Endpoint

- Number of episodes of syncope at one year (including both those identified in the medical records and self-reported episodes).

Secondary Endpoints

- Within trial cost effectiveness (cost per syncope avoided and cost per quality adjusted life year [QALY] gained), and lifetime cost per QALY at 1 and 2 years
- Number of episodes of syncope (both those identified in the medical records and self-reported episodes) at 90 days and 2 years and syncope recurrence rate at 90 days, 1 and 2 years
- Index presentation hospital admission rate and duration of hospital stay
- Patient Satisfaction (measured using a patient questionnaire) at 1 year
- Clinically significant cardiac dysrhythmia at 90-days, 1 and 2 years.
- 30 day, 1 and 2 year all cause death
- Detection of diagnostic ECG/symptom correlation (symptomatic) at 90-days, 1 and 2 years.
- Time to detect clinically significant cardiac dysrhythmia (i.e. time to clinician being aware)
- In the intervention group, duration of enhanced ambulatory ECG monitoring required to detect clinically significant cardiac dysrhythmia

Timelines



ASPIRED Project Plan 04 06 2021

TMG=Trial Management Group, DMC=Data Monitoring Committee, TSC=Trial Steering Committee, TIM=Trial Investigators Meeting

Minimum aim is 6 patients/site/month

Internal Pilot 1

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

Minimum aim is 6 patients/site/month

Internal Pilot 2

By end of study month 19	Red	Amber	Green
Total number of participants recruited	≤600	601-1299	≥1300
% recruitment of total required	27%	28-%	58%
Average recruitment rate/site/active months in the best 60% of sites *	4	5	6
Number of sites open	<10	11-20	>20