JRMO Research Protocol for Interventional Studies

Full Title	**Sickle Cell Acute Pain Pathway Evaluation (SCAPE 2): A Multi-centre Open Randomised Trial to Compare ED and Ambulatory Care Management of the Acute Sickle Cell Pain Crisis**
Short Title	**Sickle Cell Acute Pathway Evaluation 2 (SCAPE 2)**
Sponsor	Queen Mary University of London Contact person: Dr Mays Jawad Governance Operations Manager Joint Research Management Office Empire House 67-75 New Road Whitechapel, E1 1HH Phone: 020 7882 7275/6574 Email: research.governance@qmul.ac.uk
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Chief Investigator (CI)
Prof Paul Telfer
Clinical Professor of Haemoglobin Disorders and Haematology
Centre for Genomics and Child Health
Blizard Institute
Bart's and The London School of Medicine
Queen Mary University of London

Address:
Department of Haematology
Royal London Hospital
4th Floor Pathology and Pharmacy Building
80 Newark Street
London E1 2ES

Phone number: 020 3246 0338

e-mail: p.telfer@qmul.ac.uk

Co-Chief Investigator:
Dr Sanne Lugthart
Consultant Haematologist
University Hospitals of Bristol and Weston NHS Foundation Trust
Address: Bristol Haematology Oncology Centre, 22 Horfield Rd, Bristol BS2 8ED
Telephone number: 0117321121
Email address: sanne.lugthart@uhbw.nhs.uk

Co-investigators:
Dr Sara Stuart Smith
Consultant Haematologist
Kings College Hospital, London

Dr Stella Kotsiopoulou
Consultant Haematologist
Croydon University Hospitals, London

Dr Kofi Anie
Consultant Psychologist
Brent Sickle Cell and Thalassaemia Centre

Patient Representative:
Ms Carol Burt
Sickle Cell Society

List of sites
Provisional:
Kings College Hospital NHS Foundation Trust, London
Guys and St Thomas' NHS Foundation Trust, London
Birmingham University Hospitals, Birmingham
Homerton University Hospital, Hackney
Queens Hospital, Romford
Whittington Hospital, LondonManchester University Hospitals
University Hospitals of Bristol and Weston NHS Foundation Trust

Possible:
Royal London Hospital
Manchester University Hospitals
North Middlesex University Hospital

List of laboratories	No trial laboratories
Trial management centre and Randomisation centre:	Pragmatic Clinical Trials Unit (PCTU) Queen Mary University of London Professor Beth Stuart, Director, PCTU

1. Contents

2. Glossary

ACU	Ambulatory Care Units
ADL	Activities of Daily Living
AE	Adverse Event
APC	Acute Painful Crisis
APPG	All Party Parliamentary Group
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CD	Control Drug
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
DSMC	Dosing and Safety Monitoring Committee
EC	European Commission
ED	Emergency Department
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised Controlled Trial Number
JRMO	Joint Research Management Office
MA	Marketing Authorisation
MS	Member State
NEWS	National Early Warning Score
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
SCD	Sickle cell disease
VOE	Veno-occlusive pain episode

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **_Prof Paul Telfer __**

Signature: _____

Date: _____

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: _____

Signature: _____

Date: _____

4. Summary and synopsis

Short title	Sickle Cell Acute Pathway Evaluation (SCAPE 2)
Methodology	Multi-centre, open, randomised controlled trial with patients individually randomised to Emergency Department (ED) or Specialist Ambulatory Care Unit (ACU) when presenting to hospital with acute painful crisis of sickle cell disease (SCD)
Research sites	NHS hospitals covering moderate or high prevalence sickle cell populations, and providing both ED and ACU
Objectives / aims	To determine whether, in an adult sickle cell disease population, the acute painful crisis is better managed in a dedicated specialist ambulatory care unit compared with standard care in a hospital emergency department. Outcome measures will include sequential pain scores measured using visual analogue scale, time to first analgesia, opioid consumption, rate of hospital admission, time to readiness for discharge, patient health-related quality of life, patient satisfaction and cost-effectiveness.
Number of participants	228 patient episodes (114 per group).
Inclusion and exclusion criteria	Inclusion 1. Male or female participant with SCD (any genotype) 2. Age 16 or older 3. Registered in the trial centre sickle cell service with a pre-agreed personal pain management protocol uploaded on their electronic patient record 4. At least one attendance at hospital with acute pain during the past 2 years 5. Able and willing to give informed consent 6. Uncomplicated acute painful crisis requiring acute hospital treatment 7. Pain score 5 or more on a numeric rating 0-10 scale 8. Confirmed signed consent form Exclusion 1. Participants who are pregnant and more than 16 weeks' gestation 2. More than 10 hospital attendances for acute pain management in the past 12 months 3. Participant already treated for two pain episodes within the SCAPE-2 trial protocol 4. Participant has been treated for a pain episode on the trial protocol within 28 days 5. The ACU is open for less than 6 hours from time of presentation 6. Additional sickle cell complication as assessed at telephone triage or on arrival by specialist medical and/or nursing staff: a. Acute chest syndrome

	b. Acute stroke c. Priapism d. Sepsis e. Observations Temp >38.5 degrees, oxygen saturations <94% f. Any other medical issue at the trial team discretion
Statistical methodology and analysis (if applicable)	The primary outcome of pain score over the 6 hours following presentation will be compared between randomised groups using a mixed effects regression model accounting for correlation between repeated observations within participants. Analyses will be done on an intention-to-treat basis.
Study duration	36 months

5. Introduction

5.1 Background

The acute painful crisis (APC) is the most common complication of sickle cell disease (SCD). These episodes of pain are unpredictable in onset and duration and can progress to life-threatening complications, including acute chest syndrome, acute fat embolism syndrome and multi-organ failure. Severe APC may require treatment in hospital with strong opioid analgesic drugs, combined with additional supportive care measures. Careful monitoring of pain score and vital signs is essential to ensure adequate pain control, avoidance of adverse effects of analgesic drugs, and prompt intervention to manage complications[1].

Guidelines for APC management have been produced over the past two decades gathering evidence from published studies, expert opinion, and patient perspective. Unfortunately, reports from multiple sources indicate that guidelines are often not followed. Furthermore, acute care in emergency departments and on acute medical wards is suboptimal, leading to patient dissatisfaction, anxiety, and sometimes to avoidable harm. In the UK, this was recently highlighted in the report 'No one's listening' prepared by the All Party Parliamentary Group on Sickle Cell Disease and Thalassaemia (APPG)[2]. The report identified a wide range of deficiencies in services, and highlighted that the National Health Service (NHS) core values of respect and dignity, compassionate care, quality, and inclusion are not being consistently applied to people living with SCD.

For severe acute pain which cannot be managed at home, the hospital emergency department (ED) is the default location for health care intervention. This is because ED is open 24 hours per day and provides access to trained medical, nursing and allied health care professional staff who can provide urgent assessment and treatment. Challenges with ED care are well-described and generally difficult to resolve. They include lack of continuity and connection with the patient's SCD treatment team, delays in triage and assessment, reassessment, and repeat analgesia dosing. The environment is often overcrowded, noisy and stressful, and does not encourage biofeedback techniques for self-management of pain, such as relaxation and distraction. Furthermore, problematic staffing attitudes in the non-specialist setting can generate a feeling of stigma and discrimination. Patients may be labelled as drug seeking, obstructive or difficult.

Potential alternatives to current ED care include specialised units providing care in an alternative hospital-based setting. These are variously described as ambulatory units, day care units or infusion centres. For the purposes of this study we refer to them as Specialist Hospital-based Ambulatory Care Units (ACUs). The ASH guideline specified that patients on these units should be managed by a team specialised in acute SCD pain management, and should be located in a hospital with easy access to acute and intensive care facilities, recognising that occasionally patients present with acute pain together with life-threatening complications including acute chest syndrome and sepsis. This type of care provision is generally available during working hours only (Monday to Friday, 9am to 5 pm), although there are some examples of extended opening hours.[3, 4]. The unit could be entirely dedicated to SCD, or alternatively, with smaller patient populations or insufficient dedicated staff and space, the service could be embedded in a larger multi-specialty unit, such as a hospital-based haemato-oncology unit.[3, 5]

Currently, there are no randomised studies comparing standard ED care with ACU's, and relatively few observational studies, which are predominantly from a United States health care perspective. Reports in the 1990's from Montefiore Medical Centre, New York, USA[6], and the Day Centre at Birmingham City Hospital, UK[7], demonstrated satisfactory pain control, and reduction in hospital admissions, leading to significant cost savings for the service. These finding have subsequently been replicated in other centres such as an infusion clinic at Johns Hopkins Medical Centre and in the paediatric setting[3, 4, 8, 9]. A report from a day care unit in Jamaica where the unit was not located in a hospital setting highlighted the potential for harm. Fatal events were reported in a small number of patients who had been discharged home, with causes of death including acute chest syndrome and sepsis.[10]

More recently, Lanzkrom *et al* have published a study attempting to compare outcomes in infusion centres (IC) with ED[3]. The ESCAPED (Examining Sickle Cell Acute Pain in the Emergency Versus Day Hospital) study was a prospective observational study in four US cities. The investigators considered that randomly assigning to ED or IC was not possible because patients are reluctant to be assigned to ED-only care, and also because of the practical challenges of randomising during an acute VOC event. Patients would be preferentially treated in an IC during working hours, but for various reasons (low staffing, non-availability of beds, additional complications) might be allocated to care in ED. In order to account for potential bias in the type of patient and presentation being treated in IC or ED, a propensity score was applied to each event. Patients treated in an IC received parenteral pain medication substantially faster than those seen in the ED, were more likely to have their pain reassessed 30 minutes after their initial dose of parenteral medication and substantially less likely to be hospitalized than those who received care in an ED. A subsequent health economic analysis of this study suggested large savings in medical and societal costs in the US, largely driven by reduction in hospital admissions in those attending IC.[11]

One potential concern is whether opening an acute care facility might encourage patients to attend hospital for pain control rather than managing their pain at home, and this could increase hospital admissions and chronic opioid exposure. This might need to be managed by restricting access to facilities for high frequency service users. It is also not clear how the facility would be made available to patients in low-prevalence areas, with more limited specialist service provision. One proposed solution is provision of a centralised Hyper-acute Unit providing acute care for all service users in the region, and open 24 hours a day.[12] This type of unit may be suitable for service users who are local to the unit, but might entail prolonged travel for those living in other parts of the region, and might substantially increase the volume of patients requiring care and potentially hospital admission, in the hospital where the unit is hosted.

Although SCD-specific acute care facilities appear to have advantages over the ED, they are not yet standard of care and there are challenges and significant resource implications for health care providers in setting up these services. There are gaps in the existing data, which is largely retrospective and observational, and both the NICE and ASH guidelines have recommended further research in this area to compare clinical outcomes, patient satisfaction and health economic implications. A true randomised trial comparing outcomes in the ED and ambulatory care unit, including different types and size of service complemented by health economic evaluation and assessment of patient satisfaction might resolve some of the uncertainties and enable progress in optimizing care pathways.

This study aims to address these uncertainties in a prospective, randomised multicentre trial of adults with SCD presenting with acute sickle pain. The design of the study takes into account experience in conducting clinical trials in APC reviewed in a number of previous guidelines and reviews[1, 13-17], as well as the experience in the NHS setting in a dose finding and feasibility study for an oral opioid protocol, conducted at The Royal London Hospital between 2015 and 2018 (SCAPE 1)[18]. For this study protocol, SCAPE 2, multiple NHS hospitals which are able to provide both ED and ambulatory care will be involved, and patients will be allocated treatment location on arrival in hospital after telephone assessment and triage and randomisation prior to arrival. Outcomes will include a primary end point of reduction in pain score, as well as opioid usage, admission rate, patient satisfaction and health economic assessment.

5.2 Rationale

The aim of this study is to build on current evidence summarised above, by conducting a trial to make a direct comparison of two care pathways currently available in the NHS for hospital management of acute sickle pain to establish the clinical and cost-effectiveness of an ambulatory care unit in comparison with current emergency department care in NHS institutions.

Current emergency department care often fails to meet national standards, and patient experience is often poor with significant variation in care across the NHS. An improved care pathway is needed, and there is data from retrospective and prospective non-randomised studies indicating better outcomes with ambulatory care units compared to current ED care. These have largely been from the USA health care perspective and results may not be directly applicable to the NHS in England. There has never been a randomised study comparing ED and ambulatory care, and the need for well conducted randomised studies in this area have been highlighted in both the NICE and ASH guidelines on sickle pain management.

Although it seems likely that ambulatory care would be preferred by patients, it is not clear how much difference may be achieved in clinical outcomes of value to the patient, such as reduction in pain, in patient-reported quality of life, and in health care metrics, such as probability of being admitted to hospital rather than discharged home, and bed days spent in hospital for those admitted. These metrics would inform whether investing in setting up ambulatory care represents improved patient-centred outcome.

The All Party Parliamentary Group on Sickle Cell Disease and Thalassaemia report ‘No One’s Listening’ summarised experiences and opinions from health care professionals, patients and families concerning deficiencies in NHS care for acute sickle pain. One recommendation of this report was to commission work on clinical trial design to address deficiencies in evidence of effective interventions. The NHS Race and Health Observatory, an independent organization, set up to explore ethnic inequalities in healthcare and to provide recommendations to inform policymaking and facilitate change, subsequently invited applications for a grant to develop a clinical trial addressing these deficiencies. This tender was awarded to the group developing the current protocol. The core of this group consisted of members of the National Sickle Pain Group, which had been supported by the NHS England Clinical Reference Group for specialised commissioning of haemoglobin disorders, and included a range of health care professionals and patient representatives. The patient representative for this project was delegated by the Sickle Cell Society and was involved in all stages of protocol development.

The protocol development included a national workshop held in May 2023, during which relevant literature was reviewed, care models in the USA were presented, and potential trial designs were discussed. The workshop was attended by health care professionals, health service managers and commissioners, patients, carers and representatives of the Sickle Cell Society.

By undertaking the current study, emergency department and haemoglobinopathy services in NHS institutions will become more engaged in quality improvement regarding acute pain management in sickle cell disease. The study will foster a more uniform approach to acute pain management across the NHS. The proposal to study the implementation of individual pain protocols by dedicated staff in two different acute settings will help to embed two vital elements of care (individual protocols and dedicated sickle pain specialist nurses) into routine care.

In addition, the trial will answer important questions for quality of care and the cost-effectiveness of ambulatory care units such as:

-Can hospital admissions be avoided?

-Can existing NHS quality standards around acute sickle pain management be better achieved?

-Can patient quality of life and satisfaction be improved?

-Can acute care be improved with reduced health economic impact on the NHS?

6. Study objectives

6.1 Primary objective

Is acute sickle cell pain better managed in a specialist ambulatory care unit (ACU) than in ED?

6.2 Secondary objective

Is patient satisfaction improved in a specialist ambulatory care unit compared to ED?

Is management in a specialised ambulatory care unit cost-effective compared to ED?

This trial will also contribute to developing a network of NHS hospital-based clinical trials centres where a series of trials can be undertaken to study further interventions aimed at improving clinical care and patient experience in managing acute sickle pain.

6.3 Primary endpoint

- Reduction in pain score during the first 6 hours after presentation to ED and ACU using a 0-10 numeric rating scale.

6.4 Secondary endpoints

- Time to first analgesia, defined as time from presentation in ACU or ED to first dose of opioid analgesia administered. (For subjects given parenteral opioid prior to arrival in care unit, e.g. in ambulance, timing will start from one hour after parenteral analgesia given in ambulance, even if subject presents less than one hour after analgesia given in ambulance)
- Adherence to NICE guideline in safety observations (defined as proportion of hourly safety observations (respiratory rate, sedation score) taken within first 6 hours (+/- 30 mins)
- Adherence to care plan in analgesia doses (defined as proportion of analgesia doses given according to protocol within first 6 hours (+/- 30 minutes)
- Fit for discharge by 6 hours after first analgesia (defined as pain score 5 or less for at least 2 consecutive hourly assessments; no requirement for parenteral opioid for at least 2 hours and acceptable oral analgesia protocol available for use at home, NEWS score green for >2 hours, patient able to self-administer oral medication, patient mobile. All the above assessed by physician and agreed with patient)
- Time from first analgesia to fit for discharge (defined as pain score 5 or less for at least 2 consecutive assessments; no requirement for parenteral opioid for at least 2 hours and acceptable oral analgesia protocol available for use at home, NEWS score green for >2 hours, patient able to self-administer oral medication, patient mobile. All the above assessed by physician and patient).
- Cumulative dose of morphine or equivalent opioids in first 6 hours and first 24 hours
- Proportion admitted to hospital from ACU or ED
- Length of hospital stay (for those admitted to hospital), length of hospital stay Patient satisfaction with care assessed using SCAPE questionnaire 14 and 28 days after discharge
- Health economic analyses of comparative patient health-related quality of life, costs and cost-effectiveness of ACU versus ED care from the perspective/s of health and social care (NHS and PSS) and, separately, wider society
    - Costs at 28 days post-randomisation
    - QALY at 28 days post-randomisation
    - Incremental cost-effectiveness ratio

7. Study population

Eligible participants will be selected from local registers of patients attending sickle cell services which are participating in the study. Patients will be informed about the study during out-patient appointments, after acute hospital attendances or by telephone call by a member of the clinical care team and informed about the study through written and verbal information.

7.1 Inclusion criteria

All participants must meet the following inclusion criteria:

At time of consent

1. Male of female participant with Sickle Cell Disease (any genotype)
2. Age 16 or older
3. Registered at trial centre with a pre-agreed personal pain management protocol uploaded on their electronic patient record
4. At least one attendance with acute pain during the past 2 years
5. Able and willing to give informed consent

At time of presentation with APC

6. Points 1-5 patient inclusion at time of consent
7. Uncomplicated APC requiring acute hospital treatment
8. Pain score 5 or more on verbal 0-10 scale
9. Confirmed signed consent form

7.2 Exclusion criteria

Any participant who meets one or more of the following criteria will be excluded from participation:

At time of consent

1. Participants who are pregnant and more than 16 weeks' gestation
2. More than 10 hospital attendances for acute pain management in the past 12 months
3. Patient receives regular red-cell-exchanges with HbS levels < 20%

At time of the presentation with APC

4. Points 1-2 patient exclusion at time of consent
5. Participant has been treated for two pain episodes within the trial protocol.
6. Participant has been treated for a pain episode on the trial protocol within 28 days.
7. The ACU is open for less than 6 hours from time of presentation
7. Additional sickle cell complication as assessed at telephone triage or on arrival by specialist medical and/or nursing staff:
    g. Acute chest syndrome
    h. Acute stroke
    i. Priapism
    j. Sepsis
    k. Observations Temp >38.5 degrees, oxygen saturations <94%
    l. Any other medical issue at the trial team discretion

The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

8. Study design

This study is an open, multicentre randomised trial of participants 16 years or older with SCD.

Potentially eligible patients will be identified at their local trial centres by their care team and referred to their local trial centre study team, which will enable informed consent and confirm eligibility and availability of pain management protocol.

Trial centres will be NHS hospitals where SCD patients are routinely managed, and where ED and Ambulatory Care Unit facilities are both available for managing acute sickle cell pain. As required for standard of care SCD pain management in the NHS, each patient will have a pre-agreed personal pain management protocol uploaded on their electronic patient record, which reflects their usual standard care.

Subjects will be instructed to contact the local site study centre by telephone if unwell with acute pain. This telephone call will be taken by a trial nurse or doctor, who will use a trial algorithm (Appendix 2) to assess whether the patient has an eligible APC . Once this is confirmed, they will take further verbal consent to proceed with the study. The patient will then be randomised and asked to attend either ED or ACU, where they will then receive their routine protocol of care.

Patients will not be randomised if:
1. Pain can be managed without the need for hospital attendance.
2. Symptoms suggest a complicated crisis, where additional medical problems need to be managed.
3. ACU is not available at the trial centre.

The procedure for these different eventualities is illustrated in the flow-chart (Appendix 3).

<u>Randomised patients</u>
For randomised patients, their management will be implemented by their health care team for ED or ACU, using their pre-agreed pain management protocol. The trial team will not be responsible for treating the patient, but will have the following responsibilities:

- Confirmation of consent, eligibility and allocation to correct treatment location
- Pain score (0-10 numeric rating scale) at baseline and hourly for first 6 hours
- Collection of the following data:
  a) Safety data (respiratory rate and sedation score) hourly for first 6 hours (taken from hospital paper or electronic record. Record actual values and percentage of scheduled measurements.
  b) Adherence to pre-agreed pain management protocol.
  c) Cumulative opioid dose over the first six hours (from hospital paper drug chart or electronic prescribing record) and duration of episode in ED or ACU (APC episode resource use CRF).
  d) Whether the patient is admitted or discharged from ED or ACU.
  e) Any additional analgesic medication and all non-analgesic medication.
  f) Health economic data (Section 11.3)

g) Patient satisfaction questionnaire, taken 14 and 28 days after presentation using the SCAPE questionnaire.
h) Quality of life assessment; using the EQ-5D-5L tool taken on consent, presentation, 6 hours, 14 and 28 days after the presentation.
i) Length of stay for patients admitted to hospital. Defined as time from the decision to admit, to time patient leaves ward.
j) Re-attendance rate (within 7 days).
k) Complication rate (acute chest syndrome, other acute sickle complications, physician diagnosis from discharge summary).
l) Education/employment/daily activity loss (social determinants of health assessment).
m) Resource use CRF including Work Productivity and Activity Impairment Questionnaire, collected at consent, 14 days and 28 days follow-up.

Observational Arm

Consented subject may be triaged with an uncomplicated APC, but cannot be randomised for a number of reasons including:

- No trial staff available
- No available space on ACU
- ACU is closed
- Presenting within 6 hours of closure of ACU

These subjects will be managed according to normal standard care. The trial team will be responsible for a phone call 14 and 28 days after presentation and will collect clinical data the following data:

- Analgesic medication and all non-analgesic medication (from hospital paper drug chart or electronic prescribing record) and duration of episode in ED or ACU (APC episode resource use CRF).
- Quality of life assessment; using the EQ-5D-5L tool taken on consent, presentation, 6 hours and 7, 14 and 28 days after the presentation.
- Education/employment/daily activity loss (social determinants of health assessment).
- Resource use CRF including Work Productivity and Activity Impairment Questionnaire, collected at consent, 14 days and 28 days follow-up.
- Length of hospital admission, if applicable.
- Adverse events (recorded in the clinical notes and discharge summary).

9. Study procedures

9.1 Screening Procedures

Eligible patients will be identified from the local trial site's clinical database. These will be given/sent the Patient Information Sheet and invited to contact the trial PI or research nurse at the study site. Information may also be given to eligible patients at

Out-patient and Day Care visits and on recovery from acute episodes of SCD when awaiting discharge from hospital. Eligible patients will have the opportunity to discuss the trial and ask questions with investigators and trial nurses.

9.2 Informed Consent

It is the responsibility of the Investigator, or appropriately GCP trained person delegated by the Investigator as documented in the site delegation log, to obtain written informed consent from each subject prior to any participation/ study specific procedures. This should follow adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. If the participant wishes to speak to a physician (Sub-Investigator or Chief Investigator) who is present or contactable via telephone, further information can be given to the participant and any questions can be answered immediately.

Consent may be obtained by a delegated medically trained member of the research team or a delegated research nurse (any research nurse delegated to take consent will be trained in consent and have a specialised knowledge in Sickle Cell Disease). The names of all individuals entitled to obtain consent will be recorded in the delegation log.

If the research nurse has taken consent, the PI or trial physician (co-Investigator) will counter sign the consent form and document acknowledgment within the patient's notes before treatment is given. This counter signature and acknowledgment process is used where the participant is content with the information and discussions with the research nurse. In counter signing the consent form and documenting in the patient's notes prior to treatment, the physician indicates that he/she has oversight of the participant's case and planned treatment.

If for some reason, a physician (Sub-Investigator) is not accessible in person or by phone and the participant wishes to speak with them, a second consent visit should be arranged and the research nurse will not take consent at this time. As stipulated by GCP, the patient should be given ample time to consider giving their consent for the study. It is felt that 24 hours gives sufficient time for the patient to consider their participation within the study and give informed consent. The date that the Patient Information Sheet (PIS) is given to the patient must be documented within the patient's notes to ensure that sufficient time is given (minimum 24 hours).

The Investigator (or other qualified person) must explain to the potential participant that they are free to refuse any involvement within the study or alternatively withdraw their consent at any point during the study and for any reason.

If there is any further safety information which may result in significant changes in the risk/benefit analysis, the PIS and Informed Consent Form (ICF) will be reviewed and updated accordingly. All subjects that are actively enrolled on the study will be informed of the updated information and given a revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

9.3 Consent process

The consent process involves three procedures:
1. Consent
2. Checking of continued consent
3. Confirmation of consent

9.3.1 Consent

Consent will be obtained when the subject is healthy, prior to presenting with APC (Appendix 1). Consent can be obtained in any appropriate outpatient setting at the participating trial centre. Most patients will be identified during their routine haemoglobinopathy clinic appointment. Consenting patients will sign the study Consent Form. Copies of the consent form will be held by the patient, scanned onto the electronic patient record (EPR) or paper notes, and held in a secure file in the Trial Office. Patients will be given a personalised Trial Card. The name, date of birth, and hospital number and consent status will be maintained on the Enrolment Log.

9.3.2 Checking of continued consent

Presentation with APC after being consented will depend on clinical circumstances and may not occur for many months. During this time, their eligibility may have changed, or they may decide they no longer wish to take part in the trial. It is therefore necessary to confirm continued eligibility and agreement to participate for the duration of the trial.

To achieve this, consented patients will be contacted at six months (with an allowed flexibility of one month before or three months after), and six-monthly thereafter (with an allowed flexibility of one month before or three months after) in order to check against eligibility criteria and repeat verbal consent. This will be done by phone call or direct contact with the patient, and undertaken by a delegated member, who will sign and date the Consent Form for each episode of confirmation.

The updated form will replace the previous form, and sent to the patient, scanned onto the EPR and held in the trial file. Checking of consent will be recorded on the Enrolment Log and medical notes. If the re-checking of eligibility and consent is not done within the allowed time interval, the patient will be withdrawn from the study. A patient may be re-entered, but would need to be re-consented as a new patient.

9.3.3 Confirmation of consent (See Trial flow charts, 2 and 3)

Consented subjects will be instructed to call their local trial centre if they have APC and feel they need treatment in hospital. During this phone call with the local trial centre nurse, the following procedures will be done;

1. Verbal confirmation of consent and checking trial registration number
2. Confirming eligibility of APC using APC triage algorithm
3. Confirming trial eligibility against inclusion and exclusion criteria

Provided that eligibility criteria are met, the patient will be informed that they meet trial entry criteria, and will be randomized (See section 9.4).

9.3.4 Personnel taking consent

All consent and assent procedures must be done by personnel who are GCP trained, and who have undertaken trial training (recorded in the training log). Delegation for consent and assent will be recorded on the delegation log.

9.4 Randomization (See trial flow chart, Appendix, part 2 and 3)

Randomization will be done over the phone when a pre-consented subject calls the local trial centre with symptoms of APC. The procedures to be done by the trial nurse at the local trial centre to confirm consent and eligibility are listed in Section 9.2.3.

1. Verbal confirmation of consent and checking trial registration number
2. Confirming eligibility of APC using APC triage algorithm
3. Confirming trial eligibility against inclusion and exclusion criteria

If eligible for randomization, the local trial centre will next confirm the following

1. Both ED and ACU are available and resourced for treating the trial patient
2. Timing will permit 6 hours of treatment on ACU.

Once these items have been confirmed, randomization will be carried out by the local clinical trial nurse using a Queen Mary University of London Pragmatic Clinical Trials Unit dedicated online randomisation system. Participants will be randomised in a 1:1 ratio to the ambulatory care unit or hospital emergency department, stratifying by recruiting site, previous history of APC and age.

9.5 Schedule of Treatment

Routine management of APC and of complications of APC should follow standard of care at the local trial centre. This includes selection of analgesic drugs, doses and route of administration, non-opioid analgesia and non-pharmacological treatments to manage pain. Care during the APC will be given by the standard care team rather than the trial team.

9.6 Schedule of Assessment

See Table 1.

Study event	Screening	Consent and enrollment	Phone triage with APC	ED or ACU with APC	ED or ACU with APC	ED or ACU with APC	ED or ACU with APC	ED or ACU with APC	ED or ACU with APC	ED or ACU with APC	Discharge	Follow up	Follow up
Study Day			1	1	1	1	1	1				14 days	28 days
Study event number	1	2	3	4	5	6	7	8	9	10	11	12	13
Study time (hours)				0	1	2	3	4	5	6			
Eligibility	X												
Confirm individual protocol		X	X	X									
Given patient information sheet	X												
Informed consent		X											
Confirm consent			X										
Demographics [b]		X											
Medical history [c]		X	X										
Confirm inclusion/exclusion criteria			X										
Confirm eligible APC			X										
Confirm ED and ACU care available			X										
Randomisation			X										
Concomitant medication [d]		X	X										
Social determinants of health assessment		X	X								X	X	X
EQ-5D-5L [e]		X	X								X	X	X
Satisfaction with care questionnaire [f]		X									X	X	X
Vital signs [g]				X	X	X	X	X	X	X	X		
Pain score [h]				X	X	X	X	X	X	X	X	X	X
Protocol adherence [i]											X		
Time to. disposition [j]											X		
Time to readiness for discharge											X		
Cumulative opiate dose [k]											X		
Resource use CRF including Work Productivity and Activity Impairment Questionnaire[m]		X									X	X	X
APC episode resource use CRF											X	X	X
Adverse events [n]											X	X	X
Length of stay											X		
Re-attendance												X	X
EQ-5D-5L for care givers		X										X	X
Care giver questionnaire including Work Productivity and Activity Impairment Questionnaire		X										X	X

Abbreviations: ED; emergency department, ACU; ambulatory care unit, APC; acute painful crisis.

[a] 6 hours, or until discharge if before

[b] Age, sex, genotype

[c] Past medical history, to include sickle complications

[d] Collect information from the paper or electronic drug chart

[e] Provide patient with the EQ-5D-5L questionnaire. To complete on presentation and 7 days after presentation.

[f] Patient satisfaction questionnaire

[g] Hourly for the first 6 hours a per standard of care. These results should be taken from the hospital paper or electronic record. Record actual values and percentage of scheduled measurement

[h] Visual pain score to be taken by dedicated trial team. Score to be taken at baseline and hourly for the first 6 hours

[i] Use the hospital or paper record to confirm adherence to protocol

[j] Was the patient admitted or discharged from ED or ACU

[k] Cumulative opioid dose over the first 6 hours. Use data from the hospital paper or electronic drug chart.

[l] To include, but not limited to; acute chest syndrome, hospital acquired pneumonia, any other significant adverse event CTCAE grade > 3

[m] Work Productivity and Activity Impairment Questionnaire

[n] Record any AEs or SAEs in the 7 days from presentation. Use patient's notes and discharge summary.

9.7 End of Study Definition

The study will continue until data on all randomised patient episodes have been collected (including 28 days follow-up) or on completion of the 36-month period taken from time of first patient randomized. Patients will be enrolled until the end of study or until they have been treated for up to two pain episodes within the trial protocol.

9.8 Procedures for unblinding

Not applicable

9.9 Subject Withdrawal

Subjects can be withdrawn at any stage after giving consent. They should contact a trial or clinical staff member and indicate that they no longer wish to participate. This is the case whether or not they have participated in the trial during a previous APC event .

9.10 Data Collection and Follow up for Withdrawn Subjects

A first APC treated in on trial can be used for data analysis if a patient subsequently withdraws consent from continuing in the trial for a second episode.

10. Assessment and management of risk

No investigational medicinal product is being used in this trial. The analgesic drugs and any non-pharmacological agents used to treat pain will be the same as in their standard care protocol. Observations and any bloods tests or diagnostic imaging will be performed as required for standard of care, and will not be part of the trial evaluation. Subjects who would normally access ACU for their care may be randomised to ED care, and this may be perceived by the subject as a worse option.
The risks for subjects involved in the study include:

- Trial procedures delaying access to standard care.
- Trial procedures interfering with standard care and with teams implementing. standard protocols in acute care and, for those admitted to hospital, after admission to medical wards.
- Patients being discharged from hospital and not followed up according to standard care protocols once discharged.

In mitigation, both treatment arms incorporate measures to improve on current standard of care during the initial stages of hospital management of acute pain. These include allocation of individualised care plans in both arms of the study (treatment in ED or on ACU), enhanced supervision of the trial subjects, which is anticipated to improve patient safety and satisfaction and reduce harm. Prior to implementation of the trial in trial centres, and during the trial implementation period, there will be regular

training sessions for clinical trial staff and standard care staff, to ensure that trial procedures are correctly implemented.

There will also be an independent trial monitoring committee which will evaluate safety and operational problems during the entire clinical trial implementation period.

11. Statistical considerations

11.1 Sample size

The target sample size is 228 patient episodes (114 per group). This provides 90% power (with 2-sided α=0.05) to detect a mean difference between ambulatory care and hospital emergency department of 1.3 in pain scores on a 0-10 visual analogue scale at 6 hours after presentation. A difference of 1.3 in pain scores has been used as a clinically important difference in other studies.[9, 19] Data from the SCAPE trial provided an estimate of 3.2 for the standard deviation (SD) for pain scores and informed a conservative estimate of the correlation between baseline and 6-hour pain scores of 0.5[18]. The sample size allows for a conservative 15% dropout by 6 hours, informed by data from the SCAPE trial. It is anticipated that dropout will be minimised by potential use of an app to collect data including pain scores.

11.2 Method of analysis

Baseline characteristics will be summarised for each randomised group using descriptive statistics.

Pain scores at each time-point will be described for each randomised group using mean (SD), or median (interquartile range, IQR) if distributions are skewed. The primary outcome of pain score over the 6 hours following presentation will be compared between randomised groups using a longitudinal mixed linear regression model that includes all timepoints from baseline, and at each hour up to 6 hours after presentation. Performing a longitudinal analysis of all time-points using all non-missing data should allow for greater precision in the estimation of treatment effect specifically at 6 hours (the primary outcome) than an analysis of this time-point alone. The model will include fixed effects for intervention (ACU versus ED) and for the stratification factors age and previous history of acute pain crises, with random effects for site, timepoint and APC. The treatment effect of ACU versus ED will be summarised by an adjusted mean difference in pain scores with a 95% confidence interval, and significance assessed using the Wald test.

The mixed-effects model assumes that data are missing at random, i.e. results are unbiased if missingness is related to observed outcome data or stratification factors from the same participant. Patterns of missingness in the primary outcome data will be examined and a sensitivity analysis will estimate the treatment effect with missing data imputed.

The unit of randomisation is an APC, and participants may be randomised more than once within the trial. Previous studies have not shown evidence of clustering within participants in terms of outcomes for separate episodes[18], but this will be tested for in a sensitivity analysis for the primary outcome by including a random effect for participant in the regression model.

Secondary outcomes will be compared between randomised groups using methods appropriate for the type of data.

Analyses will be done on an intention-to-treat basis, including all participants according to randomised allocation.

Data collected from participants in the observational cohort will be summarised separately from those randomised into the trial using descriptive statistics.

Full details of analyses will be described in a separate Statistical Analysis Plan.

11.3 Health Economic Assessment

The economic assessment will include a comparative analysis of outcomes and costs between the current, predominantly emergency care-based, and new, with specialist unit-based, models of care and the assessment of the cost-effectiveness of the new model of care for acute sickle pain. This entails measurement, valuation and comparison of outcomes and costs of the two alternative care pathways to treat acute sickle pain. The evaluation will be performed from the NHS and personal social services (PSS) perspective as reference case[20] with additional analysis from the societal perspective.

11.3.1 Assessment of outcomes

Two outcomes, namely pain and health-related quality of life, will be used in the evaluation. These measures are among core outcomes identified for use in clinical trials of SCD interventions.[21] Pain during the first 6h is the primary clinical outcome in the trial. Effective pain management is expected to improve patient's quality of life (QoL).[22] Previous studies among patients hospitalised for acute sickle pain have shown a reduction in pain and an improvement in quality of life post treatment and discharge.[23, 24] Data on QoL will be assessed using the EQ-5D five level (EQ-5D-5L) instrument, administered to patients at initial consent, at baseline, 6 hours, 14 days and 28 days follow up. Responses to the EQ-5D will be used to calculate patient QoL utilities[25] at particular points of time by applying the UK population tariff and their quality adjusted life years (QALY) over follow-up periods using area under the curve approach.
In addition to patient related outcomes, we aim to assess care provider's quality of life outcomes. We will identify primary care giver for patients, administer EQ-5D questionnaire and estimate QALY for care givers.

11.3.2 Assessment of costs

We will identify, measure and value costs across three broad categories.

a) *Cost for the treatment of index acute painful crises*

This will have two components: cost of treatment in ED or specialist centre and, if relevant, cost of hospitalisation. The first include medication and staff costs for index pain episode treatment and we will undertake a partial micro-costing to ensure consistency in the cost estimates between the two arms. We will cost pain treatment medications used using information on type and volume of medications used and applying national drug tariffs.[26] To estimate staff costs, we will collect data on the type and pay band of the professional providing treatment and duration of episode in ED or

ambulatory care for the index pain episodes extracted from hospital electronic systems. In a scenario analysis, we use established unit costs for pain episode treatment in ED, the national schedule unit costs of emergency care to these visits,[27] and in ambulatory units, the unit costs of treating patients for acute sickle cell pain under the current commissioning and reimbursement structure of specialised haemoglobinopathy services in the NHS.

The second component is hospitalisation cost. If patients are admitted after initially presenting at ED or ambulatory care unit for treatment of acute pain episode, we will cost these admissions using the case-mix-based reference costs for the respective admissions (HRGs based). For short admissions that do not require overnight stays, we will apply respective day case unit costs and for longer admissions, we will apply the unit cost of non-elective admitted care for sickle cell with crisis.

b) Cost of other health service use

In addition to index acute pain crises treatment costs, we will assess health care resource use and costs associated with outpatient, inpatient or emergency visits and services for sickle cell and, separately, non-sickle cell related health problems. We will consent patients and request linked routine Hospital Episode Statistics (HES) data,[28] including inpatient, outpatient, emergency care and critical care episodes for the 28 days period prior to index pain episode (baseline costs) and for the 28 days follow-up period in the study. We will report use of different categories of care and their cost by applying national tariffs to the service use data.

c) Lost productivity and informal care

We will complement the base-case evaluation from the NHS and PSS perspective with additional analysis from a societal perspective, which are highly relevant for SCD patients.[29, 30] To estimate non-health care costs of patients, caregivers and society, we will collect information on employment status, days out of work, time spent to travel and access care, mode of transport and how far they travelled for treatment, transport costs to access care for acute pain treatment, and informal care received. This data will be collected using study specific Case Report Form (CRF). We will integrate the Work Productivity and Activity Impairment (WAPI) Questionnaire[31] to assess lost productivity and activity impairments.

Resource use data will be collected at consent, 14 and 28 days post randomisation covering resource use within the previous 14 days follow-up in the trial using this CRF.

Similarly, we will estimate and include costs from care givers' perspective. These include expenses incurred due to caring responsibility and the monetary value of the time they spend supporting and providing care to patients. For that purpose, we will develop a carer questionnaire that includes basic sociodemographic questions, employment information and WAPI version for care givers. We will then identify primary care providers, consent them and collect data at time points that align with patients.

11.3.1 **Analysis of cost-effectiveness**

Within-trial cost-effectiveness of ambulatory care management of acute sickle cell painful crises

For a within trial evaluation, incremental costs and outcomes between the two treatment arms will be compared and an incremental cost-effectiveness ratio (ICER)

will be estimated. Given the two outcomes, additional cost per unit of pain decreased within 6 hours and the additional cost per QALY gained will be estimated. We will assess uncertainty around the ICER using nonparametric bootstrapping with replacement by treatment allocation. The probability of the intervention being cost-effective compared to current usual care will be reported across cost-effectiveness thresholds ranging from 0 to £30,000/QALY gained.[20]

Cost-effectiveness of ambulatory care management of acute sickle cell pain episodes: impact of prevalence and ambulatory unit size and opening hours

In addition to the within trial evaluation, we will assess the value of wider adoption of the ambulatory care model. The main question the model-based evaluation will address is what is the cost-effectiveness of the ambulatory unit care pathway depending on ambulatory unit size and service configurations and prevalence of sickle cell patients in the area, and over a longer time horizon beyond the 14 days follow-up in the trial. The impact of unit sizes, configuration and demand on cost and cost-effectiveness of the new model of care will be assessed. We will develop a Markov model with 10 year time horizon and an annual cycle length. In the ED only care setting, we will assume patients who seek treatment for acute pain episodes will have access only to ED and will be in one of the two states after treatment in ED: hospitalised or discharged. On the other hand, patients with access to ambulatory units will be able to access treatment via ED or ambulatory units. We will assume those treated via ED may transition to being hospitalised, discharged or transferred to ambulatory units. Similarly, those treated via ambulatory units may transition to hospital admission or discharged. We will estimate the transition probabilities between different states using trial data. We will complement trial data with additional data drawing from relevant literature and reports[32] as well as extracts of further data from study centres.

12. Ethics

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRMO to obtain Final R&D approval.

12.1 Annual Safety Reporting

The CI will send an Annual Progress Report to the REC and the Sponsor using the Health Research Authority (HRA) template on the anniversary of the REC “favourable opinion’.

13. Public Involvement

The NHS Race and Health Observatory commissioned the development of this research protocol to improve management of acute sickle pain. The study protocol was developed after has been co-designed with input from a patient representative from the Sickle Cell Society. A conference organised by the protocol development group in May 2023 included public involvement from sickle cell disease patients. The National

Sickle Pain Group has two other patient representatives and they have had input in the trial design. The NHS Specialised Commissioning for Adults and Children with Haemoglobinopathies Clinical Reference Group has also support this trial.

14. Data handling and record keeping

14.1 Data management

- A signed protocol and any subsequent amendments
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics/MHRA submissions/approvals/correspondence
- CVs of CI and site staff
- UK regulations (GCP) course certificate of each of trial team
- Delegation log
- Staff training log
- Site signature log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial
- SAE reporting plan for the study

14.2 Source data

Source data worksheets will be supplied to all recruiting sites by the Trial Manager

The following Case Report Forms to be provided

Initial Consent

- Inclusion/Exclusion Criteria
- Background clinical data
- Usual analgesia protocol
- Date of continued consent
- QoL assessment with EQ-5D-5L
- Resource use CRF including Work Productivity and Activity Impairment Questionnaire

- Care giver questionnaire including Work Productivity and Activity Impairment Questionnaire

Presentation with APC

- Inclusion/Exclusion Criteria
- Baseline Clinical Assessment of APC
- QoL assessment with EQ-5D-5L (at presentation and at 6h)
- 1-6 hours Clinical Assessment
- 6-24 hours follow up Clinical Assessment
- APC episode resource use CRF (at end of episode at A&E or ACU)

Follow-up assessment 7-14 days after presentation

- SCAPE questionnaire
- QoL assessment with EQ-5D-5L
- Clinical Assessment
- (14d only) Resource use CRF including Work Productivity and Activity Impairment Questionnaire
- Care giver questionnaire including Work Productivity and Activity Impairment Questionnaire

Follow-up assessment at 28 days after presentation

- QoL assessment with EQ-5D-5L
- Resource use CRF including Work Productivity and Activity Impairment Questionnaire
- Care giver questionnaire including Work Productivity and Activity Impairment Questionnaire

SAE Form

CRF's will be in electronic format. Clinical information for the CRF's will be extracted from hospital paper and electronic records, and from study specific patient report forms.

Responsibility for completion of CRF's will be with delegated trial team members and will be supervised and monitored by the CI.

14.3 Confidentiality

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorized parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

The Investigator as well as the study team must adhere to these parameters to ensure that the Patient's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, each patient, at time of consent must be allocated a unique screening number by either the PI or a member of the study team

before undergoing any screening procedures. The patients initials (the first letter of their first name and the first letter of their last name) should be used as a means of pseudo-anonymizing parameters. This information should be kept on a screening log, which should be updated accordingly throughout the study. Once the patient has completed screening procedures and is enrolled onto the study, the patient will be allocated a trial number by the PI or delegated trial representative.

If any patient information needs to be sent to a third party (including sponsor) the PI and the study team should adhere to patient pseudo-anonymous parameters.
This includes the patient initials, date of birth, gender as well as the unique study ID/randomisation number. Any information that is to be collected by these third parties will utilize these coded details for any relevant documents as well as maintaining databases.

- No additional identifiable information will be collected from the trial subjects
- The Chief Investigator is the 'Custodian' of the data.
- No patient identifiable details will be transferred outside the EU
- The patient always has rights to revoke their authorization for the use of their PHI.
- The patients will be anonymized with regards to any future publications relating to this study.

14.4 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years.

15. Laboratories

Not applicable. No samples will be taken in this study.

16. Interventions and tools

16.1 Techniques and interventions

This study includes an intervention of the location of care provided to patients presenting with acute painful crises. This will a 1:1 randomisation between the ED and ACU.

16.2 Tools

The following tools with be used through-out the study (Section 9):

- Pain score (measured on a 0-10 visual analogue scale) at baseline, then I hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs[9]
- Quality of Life and Quality-Adjusted Life Year (QALY): EQ-5D-5L (ref)

- Patient satisfaction questionnaire – Satisfaction with Treatment for Pain Questionnaire (STPQ)[33]
- APC episode resource use CRF
- Resource use CRF including Work Productivity and Activity Impairment Questionnaire
- Linked participant HES data (inpatient, outpatient, emergency care and critical care)

16.3 Medicinal product

This study will not be evaluating specific medicinal products

16.4 Other biological or chemical products

This study will not be evaluating such products

17. Safety reporting

17.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

17.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression ‘reasonable causal relationship’ means in general that there is evidence or an argument to suggest a causal relationship.

17.3 Notification and reporting of Adverse Events and Reactions

If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants’ source documents, the Case Report Form (CRF), and, where appropriate, medical records.

17.4 Serious Adverse Events (SAEs) or reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

SARs will be reported to the REC where in the opinion of the CI the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

17.5 Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

SAE will be identified by the trial medical staff All Serious Adverse Event (SAEs) will be recorded in the subjects' notes, the CRF, the sponsor Specific SAE form and reported to the Joint Research Management Office (JRMO) within 24 hours of the PI or co-investigators becoming aware of the event. Nominated medically trained co-investigators will be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites.

AE's are very common findings in patients with SCD at home or in hospital because of the severe and chronic nature of the condition. For the purposes of this study the following AE's will be documented in the participants' medical notes as per standard of care, but not included on the trial CRF;

- Pain associated with the APC, including hospitalisation.
- Abnormal observations, as these are already being collected on the trial CRF.

If any of the above are classified at severe (CTCAE > 3), then they will be entered on the trail CRF.

17.6 Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However the CI will inform the sponsor and REC (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

17.7 Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

17.8 Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

18. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable. Regular monitoring of conduct of study according to protocol, any deviations and any safety issues will be done by the CI, and reported to the project steering committee at 6 monthly meetings.

19. Trial committees

Two committees will be established:

(1) The Trial Management Committee (TMC) will oversee the conduct of the trial, ensure that protocol is followed, review recruitment, consent, entry into treatment, review safety data, general conduct of the trial, termination, analysis and reporting of results. The TMC will consist of the CI and PI's, study co-ordination team, statistician, health economist. The TMC will meet regularly.

(2) The external Study Monitoring Committee (ESMC) will meet routinely to review conduct of the study and results. The remit will include

- Review engagement of sites
- Recruitment
- Adverse events and adverse event reporting
- Operational problems with implementing the trial.

The committee will include two clinicians, a specialist nurse, an NHS manager and a patient representative. The study co-ordinator will co-ordinate the meetings, assemble the documents required for review, keep minutes of the meetings and arrange feedback to the TMC.

19.1 Sponsor

The trial is sponsored by TBC.

19.2 Trial Management Group (TMG)

Title	Name	Role
Chief Investigator	Prof Paul Telfer	Chair
Co-Chief Investigator	Dr Sanne Lugthart	Member

The TMG is responsible for the study co-ordination, data quality and budget management. The TMG members listed in the table above will meet at least monthly throughout the trial. The CI will chair the TMG. Minutes will be taken by the Trial Manager and retained in the TMF. The TMG will review recruitment to the study across all study sites and will take appropriate action in the event the study recruitment rate is lower than anticipated.

19.3 Trial Steering Committee (TSC)

20. Finance and funding

Appropriate funding will be sought to be able to finance this trial.

21. Indemnity

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

22. Dissemination of research findings

Data from the trial will be presented at Sickle Cell User Group meetings, national haemoglobinopathy meetings and national and international haematology meetings. Data will also be written up and submitted for publication in haematology journals.

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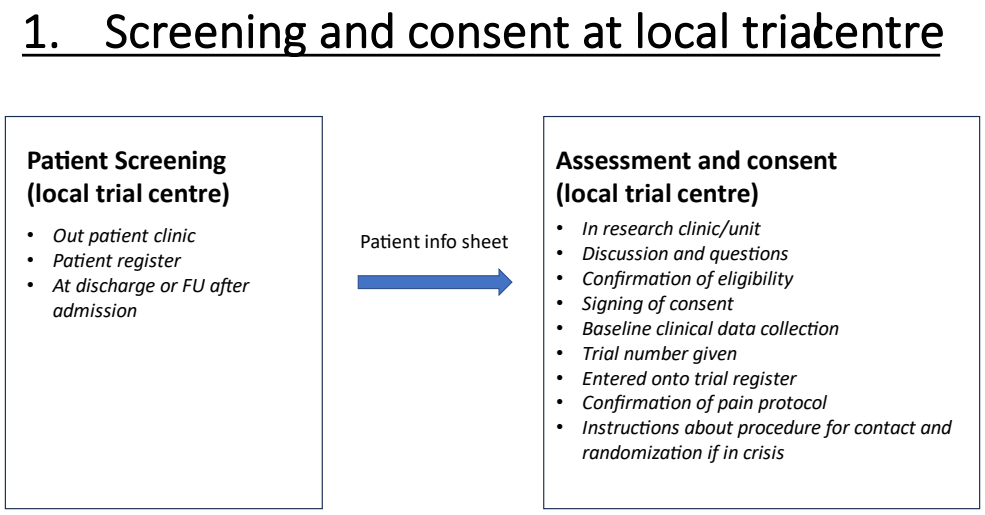
<NOTE: Before finalising the protocol, please update the table of contents (right-click any heading and select "Update field", then change to the option of "Update entire table").>

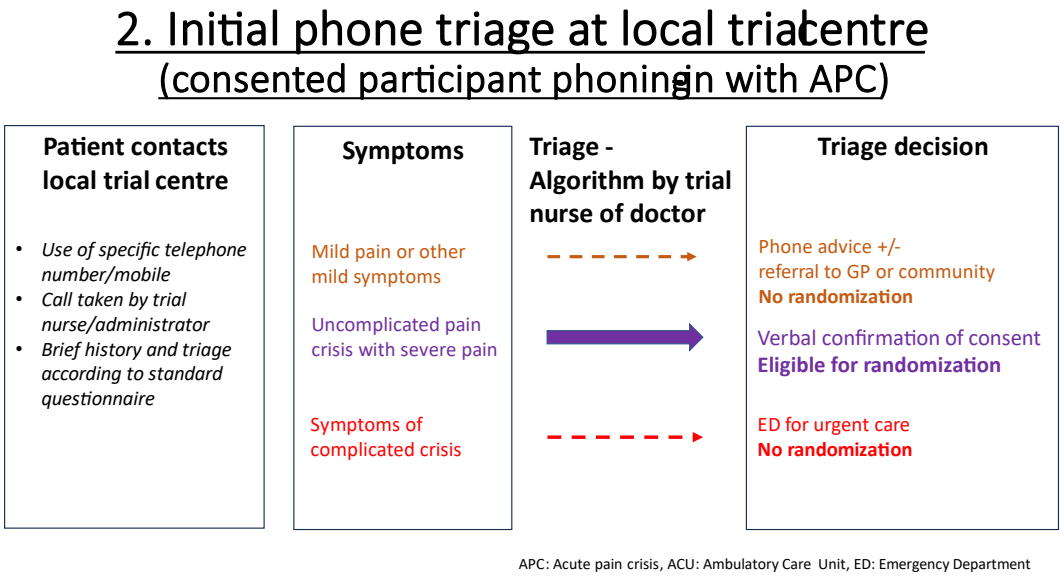
This protocol is based on JRMO Protocol template for Interventional Studies; v4.0 07.04.2022

24. Appendix

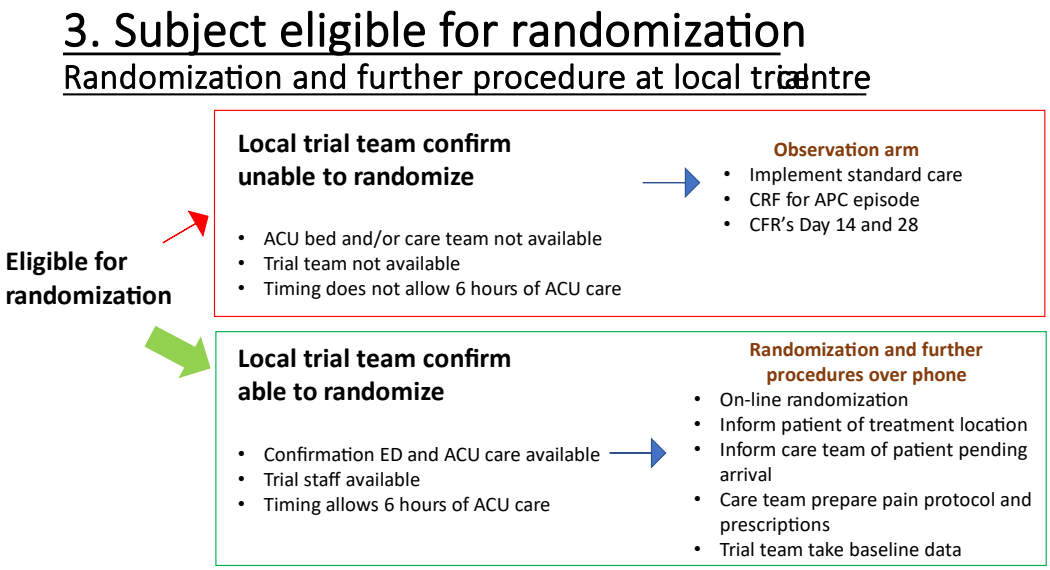
24.1 Appendix 1



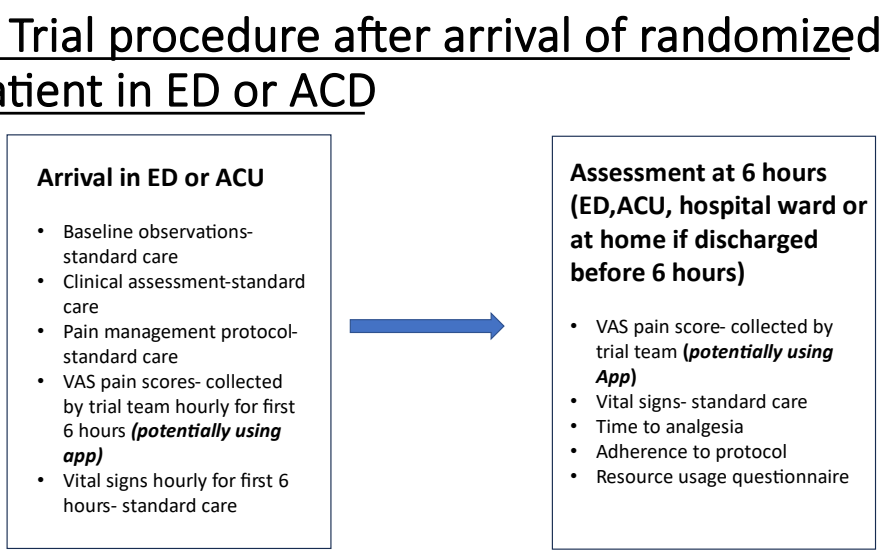
24.2 Appendix 2



24.3 Appendix 3



24.4 Appendix 4



24.5 Appendix 5