NHS RACE & HEALTH OBSERVATORY

How best to improve pain management during acute pain crises in Sickle Cell Disease?

An NHS RHO Sickle Cell Trials Working Group Report

March 2025

Executive Summary

Urgent improvements are needed in managing acute pain crises in Sickle Cell Disease (SCD), as highlighted in the All-Party Parliamentary Group Report 'No One's Listening.'

This report outlines evidence-based strategies to address these shortcomings. Key recommendations include conducting a robust clinical trial to compare emergency departments (ED) with dedicated ambulatory care units (ACUs) for managing acute sickle pain crises, refining opioid protocols, and integrating social determinants of health into trial methodologies to improve patient-centered outcomes. The report culminates in a proposed randomised trial protocol that compares outcomes in emergency departments with dedicated ambulatory care units. Securing urgent funding is critical to support this research and drive improvements in SCD care.

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1. Overview

The All-Party Parliamentary Group Report 'No One's Listening' highlighted concerns about management of people with sickle cell disease (SCD) when experiencing acute pain crisis (APC). It also acknowledged a lack of high-quality evidence for novel interventions or treatment pathways to improve outcomes and patient experience.

In June 2022, the NHS Race and Health Observatory commissioned a research project to identify potential interventions to improve the management of APC and develop a peer-reviewed randomised trial protocol to rigorously assess them. The Acute Sickle Cell Pain Research Group ("The group") comprises doctors and health care professionals who specialise in SCD, together with clinical trial specialists from the Pragmatic Clinical Trials Unit of Queen Mary University of London, and a patient representative from the Sickle Cell Society.

The group was awarded the contract for the project in November 2022 and completed their work plan between 1st January 2023 and 28th February 2024. The overall objective was to identify the most promising intervention to improve pain management during acute pain crisis in SCD, and then to develop a research protocol to assess it.

The group firstly made a comprehensive review of published literature covering a wide range of interventions which might improve management of acute pain. This review has now been published in Blood Reviews, a high impact medical journal. This document will be of value to clinicians, health service managers and researchers who are responsible for SCD care in the NHS (Appendix 1 [Literature Review Summary]).

The group identified a number of potential interventions which could be developed and tested in a clinical trial setting, and decided to prioritise the following research question: 'In an adult population, is the acute pain crisis better managed in a dedicated specialist ambulatory care unit or by standard care in a hospital emergency department?' Collaboration with the Pragmatic Clinical Trials Unit (PCTU), Queen Mary University of London facilitated planning of trial design, identification of primary end point, power calculations relating to study size, statistical analysis plan, and health economic evaluation. The group was clear that the health economic model should not only compare NHS costs of different care pathways, but would also capture the health economic burden for patients and their families/carers as a result of treatment of acute pain crisis in hospital. The draft trial protocol (Appendix 2 [Draft Clinical Trial Protocol]) is one of the deliverables from this project.

The group is actively seeking research funding to implement the trial, establish collaborations with NHS trial centers, and refine innovative outcome measures in partnership with patient groups and non-NHS organisations.

2. Project group

Members of the group are listed below:

- Professor Paul Telfer (PT): Haematologist, Barts Health NHS Trust and Queen Mary University of London
- Dr Sanne Lugthart (SL): Haematologist, University Hospitals of Bristol
- Dr Kofi Anie (KA): Clinical Psychologist, Brent Sickle Cell & Thalassaemia Centre, London North West University Healthcare NHS Trust
- Dr Stella Kotsiopoulou (SK): Haematologist, Croydon University Hospital
- Dr Sara Stuart Smith (S S-S): Haematologist, King's College Hospital
- Ms Carol Burt (CB): Sickle Cell Society and patient representative
- Professor Richard Hooper (RH): Statistician, Pragmatic Clinical Trials Unit, Queen Mary University of London
- Dr Jo Haviland (JH): Statistician, Pragmatic Clinical Trials Unit, Queen Mary University of London
- Professor Borislava Mihaylova (BM): Health Economist, Wolfson Institute of Population Health, Queen Mary University of London
- Dr Esubalew Aseef (EA): Health Economist, Wolfson Institute of Population Health, Queen Mary University of London
- Dr Ben Bloom (BB), Consultant in Emergency Medicine at Royal London Hospital and Honorary Senior Lecturer, Queen Mary University of London
- Dr Laura Aiken (LA), Clinical trials fellow and Haematology SpR, Royal London Hospital
- Dr Stephen Hibbs (SH), PhD student, Queen Mary University of London and Haematology SpR, Royal London Hospital

The involvement of two haematology trainees (SH and LA) added significant value to the project and had the welcome side effect of enhancing their clinical research training and helping to develop a clinical workforce to improve SCD care in the future.

3. Detailed Project activities

Below is a comprehensive overview of the activities undertaken in this project, each designed to address aspects of acute pain management in SCD.

The NHS Race and Health Observatory tender remit included:

1. Review of interventions aimed at improving the management of acute painful sickle cell episodes.

2. Designing an intervention or bundle of interventions that could be tested in a cluster randomised trial.

The group held weekly virtual meetings, and further activities as listed below:

National Workshop

A National Workshop, 'How can we improve care pathways and deliver care efficiently for acute sickle pain?' held at The Royal Society of Medicine on 19th May 2023.

Patient Focus Group

A patient focus group to identify social determinants of health outcomes relating to acute sickle cell pain, held at the Cavendish Conference Centre on 22nd November 2023, and supervised by KA and SH.

Online National Surveys

Several online national surveys as described below.

The primary deliverables from this work are a literature review evaluating interventions aimed at improving the management of acute painful sickle cell episodes, now published in Blood Reviews (Appendix 1 [Literature Review Summary]) and a clinical trial protocol (Appendix 2). The outcomes of the individual work-packages, as set out in the original proposal, are summarised below.

4. Summary of work-packages

Work-package 1:
Social Determinants, Equity, and Diversity in SCD Research

Incorporating social determinants of health, equity and diversity into the research programme.

Activities

1. Literature review covering social determinants of health outcomes in SCD and evidence of non-medical interventions, which can impact on these outcomes.

2. A series of on-line focus groups with patients representing the diversity of age, gender, area of residence, treatment centre and other social determinants to validate the applicability of literature review findings to the experience of patients in the NHS on topics of social determinants of health, equity and racism in health care delivery and clinical trials.

3. Preliminary work with Pragmatic Clinical Trials Unit (PCTU) to determine how social determinants of health and issues of equity can be incorporated into trial design.

Outcomes

The group undertook a literature review and findings were presented at the Royal Society of Medicine workshop (Appendix 5, slides 25-28).

Patient Focus Group

A patient focus group was then organised, and included 10 sickle cell patients. The focus group identified the predominant socio-economic issues impacting on self-management and in-hospital management of pain, and on inclusion in clinical trials (Appendix 3 [Patient Focus Group Findings]).

In-depth analysis of the testimonies from the above focus group identified themes which could be developed into patient-reported secondary outcomes in a clinical trial (Appendix 4). Further work is needed to refine and validate these items. This work might involve further focus groups and on-line questionnaires, followed by statistical analysis for validity and consistency.

Further discussions within the group resulted in inclusion of these socio-economic measures as baseline clinical characteristics to be used as predictors of outcomes in the study, as well as exploratory, secondary end points in the draft trial protocol.

Work-package 2:
Optimising Opioid Analgesia in Acute Pain Management

Optimisation of an opioid analgesia intervention for use in the ED and other clinical settings

Activities

1. Evaluation of current standard practice across NHS institutions.

2. Literature/systematic review covering analgesia protocols for acute sickle cell pain management.

3. Design of an oral opioid intervention and standard care arm for use in a core multicentre randomised controlled trial.

Outcomes

The group started by surveying current practice. A questionnaire was designed and sent out to the clinical leads of all the Haemoglobinopathy Coordinating Centres (HCCs) who were asked to coordinate responses from all specialist haemoglobinopathy teams (SHTs) and local haemoglobinopathy teams (LHTs) in their network, inclusive of adult and paediatric services. In total, 56 services (26 paediatric and 30 adult departments) in 39 centres completed the questionnaire (75% response rate). This survey demonstrated significant variation in the type of opioid used, and the preferred route of administration. The most common analgesia prescribed in adults was morphine (oral or subcutaneous). In children, oral protocols were widely used. Individual pain protocols were used in 61% of responding centres. Detailed results of the survey are presented in Appendix 6.

In the literature review, the group identified several care improvements relating to opioid use and opioid protocols which could potentially make a difference to patient experience. These included availability and accessibility of individual care plans, innovative means of delivering initial opioids to reduce time to first analgesia, and alternative means of treating background pain with opioids.

The group then identified two potential research questions relating to opioid analgesia for acute pain crisis.

1. Does intranasal fentanyl given on arrival in hospital improve initial pain management and time to analgesia in acute pain crisis of sickle cell disease?
2. For sickle cell disease patients in acute pain crisis requiring sustained analgesia, is oral modified release opioid superior to continuous opioid infusion via patient-controlled analgesia device?

These questions were further developed into a potential trial design (Trial flow chart attached, Appendix 9), but were not prioritised during the timeframe of the project. The questions remain relevant and would be suitable for reconsideration and future development.

Work-package 3:
Evaluating Non-Opioid Supportive Therapies

Evaluation of additional non-opioid supportive therapies given in the ED and other clinical settings

Activities

1. Literature review covering non-opioid supportive therapies.
2. Evaluation of current standard practice across NHS institutions with regard to non-opioid supportive therapies.
3. Focus groups to gauge patient preference on supportive therapies.
4. Prioritisation of therapies for evaluation and design of intervention for testing in clinical trials.

Outcomes

In the literature review, we found evidence that a multimodal analgesic approach, using adjuvant analgesics with different mechanisms of action might improve pain control and reduce opioid exposure. It was unclear how these agents should be combined, whether they can be given in repeated doses to sustain the opioid-sparing and analgesia effect, and whether the resources and logistics involved in formulating more complex individual management plans would result in a net benefit in health economics and patient satisfaction. We concluded that further prospective randomised controlled studies, including of adult populations, would help to resolve these uncertainties.

Patient group discussions and feedback collated by our patient representative confirmed that patients wished to have supportive therapies available in the acute care setting, as well as a calm and quiet room and warm blankets (Appendix 5, slides 30-43).

The group noted that further evaluation of one or more of these interventions in a randomised controlled trial might be valuable, but concluded that the impact on care of acute pain crisis might be less impactful than other interventions being considered. The group decided not to prioritise this topic, but suggested that data on usage of non-opioid therapies should be collected and analysed, and could become useful for a future trial comparing non-opioid interventions.

Work-package 4:
Care Pathways for Acute Pain Management

Identification and comparison of different care pathways for acute pain management

Activities

1. Literature review.

2. Evaluation of current standard practice across NHS institutions.

3. Hosting a national/international workshop to evaluate existing alternative pathways of care within NHS and other international models.

4. Design of one or more care pathway models.

Outcomes

The literature review concluded that SCD-specific ambulatory care units (ACU's) have advantages over the ED, but are not yet standard of care and the published evidence is largely limited to retrospective and observational studies. There are challenges and significant resource implications for health care providers in setting up these services. Guidelines have consistently recommended further research in this area to compare clinical outcomes, patient satisfaction and health economic implications. A true randomised trial comparing outcomes in ED and ACU, including different types and size of service and a more comprehensive evaluation of health economics and patient satisfaction might resolve some of the uncertainties. Although there would be significant practical challenges, this trial design might be feasible in a universal public funded health care setting such as the National Health Service (NHS) in the UK.

The workshop at the Royal Society of Medicine provided a further opportunity to evaluate existing ambulatory care models in the NHS and in the USA. Presentations from Hammersmith Hospital, King's College Hospital, University Hospitals of Bristol and Croydon University Hospitals gave the UK perspective on ambulatory care and ED improvements (Appendix 5).

The group had several discussions with NHS England commissioners and managers. Dr Dianne Addei (Senior Public Health Advisor, National Healthcare Inequalities Improvement Programme, NHS England) was consulted about parallel planning of pilot hyper-acute units for sickle pain management. There was a general agreement that NHS England plans to establish a number of new hyper-acute units in England may increase the number of clinical trial sites and enhance the feasibility of a clinical trial.

The group considered alternative care pathways aimed at enhancing rather than bypassing ED. One suggestion was to develop and evaluate the role of an acute sickle pain nurse specialist, who would coordinate management in ED and provide more one-to-one support for patients in ED, rather like the model of a post-surgery recovery nurse. This led to a survey, confirming that this role had not yet been developed as a standard model of care in the NHS (Appendix 9). Consequently, the group made an application for pilot funding to further explore the role through a Health Inequalities Targeted Call (Appendices 10 and 11). Unfortunately, this bid was not successful; however, the concept remains relevant and would be suitable for reconsideration and future development outside of the current project.

Work-package 5:
Trial Design for Comparing Interventions in Acute Pain Management

In this part of the project we will bring together the findings and outcomes of WP1-4 to design a multicentre randomised controlled trial (RCT) with the objective of comparing different interventions in management of acute pain in SCD.

Outcomes

The group met with the National Institute of Health Research (NIHR) funding stream leads to enquire which of the research questions identified in the above work-packages might be suitable for NIHR funding. The group was advised that the question: 'In an adult population, is the acute pain crisis better managed in a dedicated specialist ambulatory care unit or by standard care in a hospital emergency department?' could be addressed in the framework of a pragmatic clinical trial with a randomisation to standard ED care or care on a dedicated ACU. Ethical implications were also discussed, including the issue of randomising patients to ED rather than ACU, when ACU is generally preferred by patients. The group reached a conclusion that the research question was of high importance for the NHS. Our patient representative consulted widely in user groups and felt that patients would be willing to participate if the end results were a beneficial change across the NHS.

A trial protocol was then drafted, using the Queen Mary University of London and Barts Health NHS Trust Joint Research Management Office protocol template (Appendix 2 [Draft Clinical Trial Protocol]). Important elements of the proposed trial are listed below:

- 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.

- This is a pragmatic clinical trial, and will not involve any new drug intervention.

- The trial will require implementation of the current standard of care for APC whether delivered in ED or ACU. This includes access to and implementation of the patient's pre-agreed individual analgesia care plan

- There are a few innovations in the care pathway which are required for implementation of the protocol and which should benefit patients whether randomised to ED or ACU. For instance, we propose a local facility for telephone contact with the trial/clinical team prior to admission for evaluation, advice and decision about randomisation. There will be a management algorithm to guide the telephone team in advising the patient. Furthermore, once randomised over the phone, the treatment team (whether ED or ACU) will be forewarned of the patient's arrival, and this will help in preparing analgesia prescriptions, bed space etc.

- Change in pain score between 0 and 6 hours after arrival in hospital was chosen as the primary end point. This metric is relevant to patient experience, and has been used in several other trials of acute pain in SCD.

- The power calculation gave a sample size of 228 events (114 per randomised group), and this was considered feasible for a 3-year, multicentre study and would be likely to provide sufficient data for the health economic analysis.

- Secondary end points include a range of parameters relevant to patient experience of care, as well as health service outcomes relevant to NHS planning.

The group then undertook a sequence of surveys to identify SCD centres in the UK which provided both ED and ambulatory care and would be suitable trial centres. Based on these surveys, at least 6 potential trial centres have been identified (Appendices 7 and 8).

5. Recommendations

It is strongly recommended that:

- Potential trial centres form collaborative partnerships to further refine and optimize the trial protocol, ensuring consistent and robust implementation across sites.

- NHS Digital and commercial software providers create a user-friendly smartphone or tablet application to facilitate efficient data entry, covering baseline data, pain scores, quality of life assessments, and patient satisfaction metrics.

- The urgent funding critical to support this research and drive improvement in SCD care is identified.

Appendix

Literature Review

Psychological Interventions
Kofi A Anie
London North West University Healthcare NHS Trust

Psychoeducational & Self-Regulation

Patients	Children: N=39	Children, Adolescents: N=57	Children & Adolescents: N=8	Children, Adolescents & Adults: N=37
Intervention	**Group:** Families 6 Sessions Psychoeducation vs None	**Inpatient Group:** 3 Sessions Psychoeducation	**Individual:** 6 Sessions Biofeedback & Relaxation	**Individual:** 18 Mon Sessions CBT with Self-Hypnosis vs None
Outcome	Improved SCD Knowledge	Improved pain management knowledge	Reduction in Pain & Analgesia Use	Reduction in Pain Days & Analgesia Use
Reference	Kaslow et al. Fam Syst Health. 2000;18(4):381-404.	Sil et al. Pediatr. Blood Cancer 2021; 68(6):e29013.	Cozzi et al. Biofeedback Self Regul. 1987;12(1):51-61.	Dinges et al. Int J Clin Exp Hypn. 1997;45(4): 417-32.

Cognitive behavioural therapy (cbt)

Patients	Adults: N=59	Children: N=65 Adolescents: N=46	Adults: N=35	Adults: N=30
Intervention	**Group:** 8 Sessions CBT vs Attention Placebo vs None	**Individual:** 6 Sessions CBT vs Art Therapy vs Attention Placebo	**Individual:** 6 Sessions CBT (manual assisted) vs None	**Individual:** 8 Sessions cCBT with Care Coach Support vs None
Outcome	Reduced Emotional Pain Component	Reduced Healthcare Utilisation*	Reduced Anxiety Improved Coping	Reduced Depression at 6mons & Improved Daily Pain
Reference	Thomas et al. Br J Health Psychol 1999;4:209–29.	Broome et al. J Nat Black Nurses Assoc 2001;12(2):6–14.	Anie et al. Behav Cogn Psychother 2002;30:451-8	Jonassaint et al. Trans Behav Med 2020;10(1):58–67.

Summary

Limited evidence for psychological interventions in sickle cell disease Mostly cognitive behavioural therapy More research is required – ongoing studies.

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