Application: Acute sickle pain nurse specialist management of sickle crisis in ED

Paul Telfer - p.telfer@qmul.ac.uk
Health Inequalities Targeted Call 2023

A. GDPR Notification

Completed - 11 Jul 2023

GDPR Notification

NB. Please can you make sure you set the site language to English (British) by clicking on your user name (top right hand corner on the menu bar), selecting My Account and updating default language settings to English (British).

Introduction

The NHS Innovation Accelerator is hosted at UCLPartners. UCL Partners (“we” “us”, or “our”) respects your privacy and is committed to protecting your personal data. Please read this Privacy Notice carefully – it describes why and how we collect and use personal data and provides information about your rights. It applies to personal data provided to us, both by individuals themselves or by third parties. We keep this Privacy Notice under regular review. It was last updated on 28 July 2020.

About us

UCLPartners is an academic health science partnership that brings together people and organisations to transform the health and wellbeing of the population. UCLPartners, a company incorporated in England and Wales (06878225), is the entity that determines how and why your personal data is processed. This means that UCLPartners is the ‘controller’ of your personal data for the purposes of data protection law.

Purpose

Personal data is collected for the purposes of the NHS Innovation Accelerator application process so that we can contact you as to the outcome of your application. **If you are successful in your application, then the contact details provided will be added to the NIA mailing database, for the purpose of providing you with programme related information and communications.**

Personal data that we collect about you

Personal data, or personal information, means any information about an individual from which that person can be identified. It does not include data where the identity has been removed (anonymous data). In order to process your application, we will collect, use, store and transfer the following fields of personal data:

- Name (and title)
- Job title
- Address
- Telephone number
- Employing organisation
- Email address

Criminal records data

In certain circumstances, we may process data relating to your criminal convictions and offences. Access to, and the sharing of, this information is also controlled very carefully.

Our lawful basis for processing

Our basis for processing your personal data is ‘Legitimate Interests’. Our basis for processing your criminal convictions data is ‘Employment law obligations’. We will only process criminal convictions information where this is necessary so that we can meet our obligations in the field of employment law.

How we use your personal data

We will only use your personal data when the law allows us to. We will use the personal data you have provided to process your application for the NHS Innovation Accelerator Programme. If, as part of your application, you consent to joining the NIA Mail List, then your data will be processed in order for UCLPartners to send you:

- Invitations to workshops and talks about improvement topics
- Notification of and requests to circulate information on programmes
- Any information available for support from the NIA Programme

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Who we share your personal data with

Your personal data will be collected and processed primarily by our staff. We may have to share your personal data with the parties set out below for the purposes outlined in this notice

• NHS England – their privacy notice can be found here https://www.england.nhs.uk/contact-us/privacy-notice/

• Members of the AHSN Network (including the 15 Academic Health Science Networks) - their privacy notice can be found here http://www.ahsnnetwork.com/privacy/

• momentive (previously Survey Monkey Apply and Fluid Review) – the 3rd party software used to collate and review your application – their Privacy Notice can be found here. We require all third parties to respect the security of your personal data and to treat it in accordance with the law.

We do not allow our third-party service providers to use your personal data for their own purposes – we only permit them to process your personal data for specified purposes and in accordance with our instructions.

Data security

We have put in place appropriate security measures to prevent your personal data from being accidentally lost, used or accessed in an unauthorised way, altered or disclosed. We have established procedures to deal with any suspected personal data breach and will notify you and any applicable regulator of a breach where we are legally required to do so.

International transfers

Survey Monkey Apply is used as the application platform for applications, and therefore your data will be shared with Survey Monkey Apply in order to store applications. Survey Monkey Apply servers are based in Canada, and Survey Monkey Apply operates under ‘Privacy Shield framework’. Therefore, please note that your data will be transferred outside of the EU/EEA. Survey Monkey Apply will process your personal data according to their Privacy Policy.

Data retention

We will only retain your personal data for as long as necessary to fulfil the purposes we collected it for, including for the purposes of satisfying any legal, accounting, or reporting requirements. If you are successful, your data is transferred to a restricted access folder at UCLPartners.

We will keep your personal data whilst we are assisting you and for a period of 1 year after the date on which your participation in the NHS Innovation Accelerator has completed – either as an active “Fellow” or as an “Alumni”. The files are then destroyed.

If your application is unsuccessful then your data will be retained for a period of 6 months, after which it will be deleted from UCLPartners and Survey Monkey Apply servers, however, it will be held in Survey Monkey Apply backups for a maximum period of 12 months following deletion.

Your rights

Under certain circumstances, you may have the following rights under data protection laws in relation to your personal data:

• Right to request access to your personal data;

• Right to request correction of your personal data;

• Right to request erasure of your personal data;

• Right to object to processing of your personal data;

• Right to request restriction of the processing your personal data;

• Right to request the transfer of your personal data; and

• Right to withdraw consent. If you wish to exercise any of these rights, please contact us using the details set out below.

Contacting us

You can contact UCLPartners by writing to GDPR, UCLPartners, 3rd Floor, 170 Tottenham Court Road, London, W1T 7HA. Please note that UCLPartners has appointed a Data Protection Officer, Rebecca Graham. If you have any questions about this Privacy Notice, including any requests to exercise your legal rights, please contact our Data Protection Officer using the details set out below: Rebecca Graham, gdpr@uclpartners.com

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Complaints

If you wish to complain about our use of personal data, please send an email with the details of your complaint to gdpr@uclpartners.com so that we can look into the issue and respond to you. You also have the right to lodge a complaint with the Information Commissioner's Office (ICO) (the UK data protection regulator). For further information on your rights and how to complain to the ICO, please refer to the ICO website at https://ico.org.uk.

Please confirm that you have read and understood the details provided above.

Yes

The Academic Health Science Networks (AHSNs) may, on occasion, perform horizon scanning exercises in partnership with NHS England, Integrated Care Systems and other public healthcare providers to understand what innovations are currently available to address certain priorities affecting the health and social care system. They may request from the NIA the following data from recent applications made to the NIA:

- Applicant's first name
- Applicant's surname
- Applicant's email address
- Applicant's contact number
- Applicant's innovation name
- Innovation / company website address

Please confirm if you consent to the 15 Academic Health Science Networks contacting you using the details provided to them during the horizon scanning exercise detailed above.

Yes

Please confirm if you consent to the 15 Academic Health Science Networks contacting you using the details provided to them during the horizon scanning exercise detailed above.

Yes

B. Due Diligence

Completed - 11 Jul 2023

B. Due Diligence

NB. Please can you ensure you set the site language to English (British) by clicking on your user name (top right hand corner on the menu bar), selecting My Account and updating default language settings to English (British).

Please be aware that the NIA will:

- **Carry out checks on social media and other searches to identify negative feedback related to the reputation/public perception of the organisation being supported through this call.**
- **Complete a review of your innovation's competitors in the market**
- **Consider your application in light of these findings**

If successful, SMEs will also be required to provide the following (NHS organisations/ public sector organisations do not need to provide this):

- **3 years of annual accounts**
- **List of directors/ advisors**
- **Annual report**

B1. Do you have any unspent criminal convictions?

If you have answered yes, please provide further details. Answering 'yes' to the question will not necessarily bar you from the programme. This will depend on the information you provide and whom and where the innovation will be used.

No

B2. Is your organisation NHS or a public sector organisation?

Please note that if you answer Yes to this question and represent an NHS or a public sector organisation you do not need to answer questions B3 and B4.

Yes

C. Applicant Information

Completed - 13 Jul 2023

Applicant Information

NB. Please can you ensure you set the site language to English (British) by clicking on your user name (top right hand corner on the menu bar), selecting My Account and updating default language settings to English (British).

The questions in this section must be completed before you are able to commence the full application. If you have any queries please contact the NIA Team at nia@uclpartners.com.

Contact Information

C1a. Applicant's name	Paul
C1b. Applicant's surname	Telfer
C2. Job title	Clinical Professor of Haemoglobin Disorders and Haematology.
C3. Employing organisation/other	Bart's Health NHS Trust
C4. Postal address	Department of Haematology, Royal London Hospital, 4th Floor Pathology and Pharmacy Building, 80 Newark Street
C5. Town / City	London
C6. Postcode / Zip Code	E1 2ES
C7. Country	United Kingdom, The
C8. Contact email	p.telfer@qmul.ac.uk
C9. Contact telephone number	07906311482
C10. Where did you hear about the NHS Innovation Accelerator call	Other

If other, please specify:

NHSE Health Inequalities, NHS Race and Health Observatory

C11. Reasonable adjustments:

Please state any reasonable adjustments based on a disability or long-term health need(s) that you might require during the recruitment process or if you are successful in gaining a Fellowship place. The answer to this question will help us to better support you through the recruitment process and will not form part of the assessment process.

None

D. Employing Organisation Information

Completed - 13 Jul 2023

Employing Organisation Information

NB. Please can you ensure you set the site language to English (British) by clicking on your user name (top right hand corner on the menu bar), selecting My Account and updating default language settings to English (British).

The questions in this section must be completed before you are able to commence the full application. If you have any queries please contact the NIA Team at nia@uclpartners.com.

D1. Employing Organisation

Barts Health NHS Trust

D2. Is your organisation NHS or a public sector organisation?

This field is pre-populated by the answer you supplied in B2.

Please note that questions (3 – 14) are relevant to those applicants that represent a registered company whether for profit or not for profit. This does not need to be completed for NHS or public sector organisations.

NHS Organization

Contact Information

D3. Organisation Postal address	N/A
D4. Organisation Town / City	N/A
D5. Organisation Postcode / Zip Code	N/A
D6. Organisation Country	United Kingdom, The
D7. Website address (if appropriate)	N/A

D8. Please provide a summary of your organisation. (Max 100 words)

N/A

D9. Company/charity registration number

N/A

D10. Date incorporated

13/07/2023

D11. Company type

Other, please specify...: NHS

D12. How many employees does your organisation have?

0

D13. Please provide details of the following for your organisation in the 2022/23 financial year:

Projected revenue	N/A
Projected costs	N/A
Projected profit / loss after Tax	N/A
Net assets / liabilities	N/A

D14. Please detail your organisation's funding / ownership structure (Max 100 words)

N/A

E. Application Form

Completed - 26 Jul 2023

Application Form

NB. Please can you ensure you set the site language to English (British) by clicking on your user name (top right hand corner on the menu bar), selecting My Account and updating default language settings to English (British).

Please complete all questions on the application form. The application form is divided into nine sections to capture information about:

Section 1: Basic information

Section 2: Market research and current care pathwa

Section 3: Current care pathway

Section 4: Testing with users

Section 5: Regulations, standards and certifications

Section 6: Intellectual property

Section 7: Revenue model

Section 8: Cost and savings

Section 9: Deployment

Each question has a maximum word limit that you will not be able to exceed when entering your response into the system. Your application should demonstrate criteria in all sections of the application.

Section 1. BASIC INFORMATION

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1. Are you currently receiving any support for your innovation?

This can include any UK funding to support the development of your innovation.

(150 word limit)

Currently only NHS funding of staffing and facilities to support standard care for sickle cell disease.

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2. Are you involved with any Accelerated Access Collaborative programmes?

Select all that apply.

Responses Selected:

No

3. What problem is your innovation trying to solve?

Include the current consequences of the problem. For example, the process of checking a patient's pulse to determine if there is atrial fibrillation using a finger and a watch is inherently inaccurate. Using this method approximately 25% of patients are not referred to secondary care who should be (false negative) and 15% of patients who are referred are referred unnecessarily (false positive). For those patients who are not picked up at this stage, their underlying disease will progress before being correctly diagnosed.

(500 word limit)

Acute severe pain is the commonest complication of sickle cell disease (SCD) and presents a significant challenge for NHS resources. Hospital admissions with SCD are increasing approximately 2-fold every ten years. At the Royal London Hospital there were about 1500 ED attendances with acute sickle cell in the year 2022-3, almost all of which were for acute pain. In smaller units serving lower prevalence areas, ED episodes may be less than one per day.

Severe pain requires prompt, effective, safe and compassionate treatment. Strong opioid analgesic drugs are nearly always needed, together with careful monitoring to detect early signs of progressive organ dysfunction (e.g. the acute chest syndrome) and for adverse effects of medication. Standard treatment has been described in several evidence-based guidelines, including the NICE 2012 guideline 'Managing acute painful episodes in hospital'.

Poor quality care in ED is almost universal in the NHS, with evidence of failure to meet NICE standards. Lack of compassionate care is reported in research publications, national peer review programmes, and in a report commissioned by the All-Party Parliamentary Group on Haemoglobin Disorders.

Alternative care models by-passing ED have been proposed to address persisting problems in care delivery. Ambulatory care units have been shown to provide better outcomes, but are currently only available in about 14% of SCD services in England.
NHS England is currently setting up pilot hyper-acute units but these may not be universally applicable and some large units have not been able to meet specifications. Alternative care pathways to enhance the quality of care in ED should also be considered. We are proposing a model in which an Acute Sickle Pain Nurse Specialist (ASPNS) supervises care and accompanies the patient through their initial pathway of treatment. Evidence for the effectiveness of this model comes from a pilot during a clinical trial at the Royal London Hospital.

4. Give an overview of how your innovation works.

If this is or might be a medical device, include the intended purpose statement.

For example, GPs will identify patients with suspected atrial fibrillation from their history and reported symptoms. This innovation is a portable device that patients wear over a 7-day period. The device will monitor the patient's heart rate continuously whilst they are wearing it. GPs will need to be trained in using the device and interpreting the results. GP practices will need to store the device and consumables.

(300 word limit)

The Acute Sickle Pain Nurse Specialist (ASPNS) improves care and patient experience at three stages of the care pathway of an acute sickle cell crisis. (1) Initial evaluation and triage of the patient at home, by phone or videocall, using a standardised acute sickle cell crisis triage algorithm (2) Accompanying the patient during the ED stage of care, ensuring delivery of the personalised care plan, meeting national quality standards of timeliness of analgesia, assisting ED staff in administering analgesia, performing regular observations and providing non-pharmacological therapies to assist with pain management. (3) ensuring that the management plan for continuing care after discharge home from ED or admission to hospital ward is correctly implemented. This would include confirming analgesic prescriptions and follow-up arrangements.

The ASPNS will facilitate liaison between the SCD treating team, ED staff and primary care. There will also be an important role in educating medical, nursing and paramedical staff in management SCD patients in acute crisis in ED.

This model of care is proposed as a complementary and alternative pathway to the pilot scheme currently being explored by NHSE for bypassing ED by establishing pilot regional hyper-acute units. This ED model utilises existing ED facilities which are open 24 hours per day. It avoids the need to transplant an SCD patient to a potentially distant unit to manage a frequently recurring event. An ASPNS could be part of a more general role for a SCD nurse specialist in low prevalence areas, where ED attendances by SCD patients are infrequent.

5. What are the benefits or impact of your innovation for patients and people?

Select all that apply.

Responses Selected:

Reduces mortality
Reduces need for further treatment
Reduces adverse events
Enables earlier or more accurate diagnosis
Reduces risks, side effects or complications
Prevents a condition occurring or exacerbating
Avoids a test, procedure or unnecessary treatment
Increases self-management
Increases quality of life
Enables shared care
Alleviates pain
Reduces inequalities

6. What are the benefits or impact of your innovation for the NHS and social care?

Select all that apply.

Responses Selected:

Reduces the length of stay or enables earlier discharge
Reduces need for adult or paediatric critical care
Reduces emergency admissions
Improves patient management or coordination of care or services
Takes less time
Is cost saving
Increases efficiency
Improves performance

7. Have you estimated the carbon reduction or savings that your innovation will bring?

All NHS suppliers will be expected to provide the carbon footprint associated with the use of their innovation, as outlined in the Delivering a Net Zero NHS report.

If this is something you are unsure of, the NHS Innovation Service can support you with this.

Not yet, but I have an idea

7.2 (If no) Explain how you plan to calculate this.

(100 word limit)

This innovation will be implemented in hospital emergency departments and will not have any direct or indirect effect on the hospital's carbon footprint.

8. Do you have or are you working on a carbon reduction plan (CRP)?

All NHS suppliers will require a carbon reduction plan (CRP), as outlined in the NHS Suppliers Roadmap plan.

No, I do not have one

9. Have you completed a health inequalities impact assessment?

By this, we mean a document or template which asks you about the impact of your innovation on health inequalities. One example is the Equality Impact Assessment Standard produced by the NHS Race and Health Observatory.

Yes

9.1 If yes, upload the health inequalities impact assessment, or any relevant documents

Equities questionnaire.docx

Filename: Equities questionnaire.docx **Size:** 14.2 kB

10. Do you have any evidence to show the impact or benefits of your innovation?

Yes

10.1 (if yes) What type of evidence or research do you want to submit?

Evidence can include clinical and economic evidence, as well as service evaluation, environmental and social impact or other proven benefits such as staff and system benefits. You will be able to add several pieces of evidence one at a time. We will ask about user testing and regulatory approval in later sections.

Evidence of clinical or care outcomes

10.2 What type of evidence do you have?

Responses Selected:

Non-randomised non-comparative data published in a peer reviewed journal

10.3 Write a short summary of the evidence.

Give a brief overview that covers the scope of the study and its key findings.

(200 word limit)

Health inequalities with regard to treatment of sickle cell disease in the NHS have been highlighted in the All-Party Parliamentary Report 'No one's listening' and are being addressed through several initiatives currently undertaken by NHS England, as well as in projects commissioned by the Race and Health Observatory.
Inequalities with regard to hospital management of acute pain in ED have been demonstrated in several international publications, for instance comparing metrics of SCD pain to renal colic pain. Another example from the NHS is the disparity between management of acute post-operative surgical pain and acute sickle pain. Acute post-operative pain would typically be managed by an anaesthetist and on-to-one recovery nurse.
We have evidence from the SCAPE study that one-to-one nursing enhances the care pathway for acute sickle pain in ED. Attached documents are the publication of the SCAPE trial, and patient comments on benefit of one-to-one nursing in the study.

10.4 Upload any documents that support this evidence

Telfer 2021 BJ Pain.pdf

Filename: Telfer 2021 BJ Pain.pdf **Size:** 393.9 kB

11. Are you currently collecting evidence, or have plans to collect evidence?

Yes

11. 1 If yes, write a short summary of your ongoing or planned evidence gathering.

(200 word limit)

The ASPNS model is being discussed in various clinical fora, including the Clinical Reference Group for Specialised Commissioning in Haemoglobin disorders, the National Haemoglobinopathy Panel, and the National Sickle Pain Group. All of these groups have multi-professional (including nursing) representation and patient representatives.
At present, ASPNS involvement in ED pain management is not standard care and very sporadically available, as it is not considered part of the SCD Nurse specialists role.
The aim is to advocate for better definition of this role and incorporating the role into the standard specifications of a service. This would require education resources, further training and expansion in personnel.
We propose the next stage would be to implement the model described in this application in a small number of pilot units. Metrics to be collected in the pilot would include time to first analgesia, adherence to protocol, proportion discharged from ED vs admitted to hospital, patient satisfaction and health economics.
Funding for these pilots would be sought through NHS improvement schemes, and local business plans for institutional service developments.

11.2 Upload any documents relevant to this evidence collection

Section 2. MARKET RESEARCH AND CURRENT CARE PATHWAY

12. Have you conducted market research to determine the demand and need for your innovation in the UK?

By this, we mean any research you have done to determine the market opportunity for your innovation. You will be able to explain any testing you have done with users later in the record.

Yes

12.1. Describe the market research you have done, or are doing, within the UK market.

There are different methodologies available and could include a mix of the following:

- *In-depth interviews*
- *Focus groups*
- *Telephone interviews*
- *Patient record forms*
- *Computer-assisted telephone interviews*
- *Online surveys*
- *Market research online communities*
- *Ethnography*

(200 word limit)

Further support for this model is being sought from clinicians through an on-line survey of all services treating SCD in UK and patients' views are being solicited through an on-line survey with our patient representative on the application group as well as through the Sickle cell society.

13. Which option best describes your innovation?

A more cost-effect alternative to those that already exist

14. What competitors or alternatives exist, or how is the problem addressed in current practice?

Include how your innovation is different to the alternatives in the market.

(250 word limit)

Management of acute SCD pain through standard ED pathways is the current default. In some centres, collaboration between ED and SCD services have brought about improvements in outcomes and patient satisfaction, and most hospital trusts have developed an ED plan to improve SCD pain management in response to the APPG report.
A survey by the National Sickle Pain Advisory Group estimates that about 14% of units are able to offer ambulatory care in a specialised unit as an alternative to ED care, however, these units are generally open only between 9am and 5 pm Monday to Friday, and therefore do not accommodate patients presenting outside of working hours. The NHS England pilot scheme of regional, 24 hour per day hyper-acute units may address some of the problems in care, but it is likely that there will be a limited number of these units in the initial pilot phase.
There is an urgent need to examine alternative care pathways, and to examine how the ED setting can be optimised for SCD pain management. Also to ensure equity of access to patients who would be unable to travel to a regional hyper-acute unit.

Section 3. CURRENT CARE PATHWAY

15. Does your innovation relate to a current NHS care pathway?

An NHS care pathway outlines the entire patient journey and the actions taken in different parts of the healthcare system. It's key to understand the existing routines of clinical and care professionals, administrators and others who will be impacted by your innovation.

If your innovation does not play a role in the delivery of care, select 'does not form part of a care pathway'.

There is a pathway, and my innovation changes it

16. Describe the potential care pathway with your innovation in use.

Focus on any areas that will be impacted by introducing your innovation to the care pathway.

(200 word limit)

See attached flow chart. We propose to further pilot the role in specialised Haemoglobinopathy centres in England. The Acute Sickle Pain Nurse Specialist (ASPNS) can improve care and patient experience at three stages of the care pathway of an acute sickle cell crisis. (1) Initial evaluation and triage of the patient at home, by phone or videocall, using a standardised acute sickle cell crisis triage algorithm (2) Accompanying the patient during the ED stage of care, ensuring delivery of the personalised care plan, meeting national quality standards of timeliness of analgesia, assisting ED staff in administering analgesia, performing regular observations and providing non-pharmacological therapies to assist with pain management. (3) ensuring that the management plan for continuing care after discharge home from ED or admission to hospital ward is correctly implemented. This would include confirming analgesic prescriptions and follow-up arrangements.

Section 4. TESTING WITH USERS

17. Have you involved users in the design process?

This includes involving patients or the public, carers, clinicians or administrators in the design process, including people with different accessibility needs.

Yes

18. Have you tested your innovation with its intended users in a real life setting?

Do not include any testing you have done with users in a controlled setting.

Yes

19. Which groups of intended users have you engaged with?

Responses Selected:

Clinical or social care professionals working in the UK health and social care system
Patients
Service users
Carers

20. What kind of testing with users have you done?

This can include any testing you have done with people who would use your innovation, for example patients, nurses or administrative staff.

Describe the testing and feedback received.

Provide a brief summary of the method and key findings. You can upload any documents that showcase your user testing next.

(200 word limit)

We have two examples relevant to this application.
(1) A a study to develop a questionnaire to quantitate patient satisfaction with pain management in hospital (See publication Elander et al, 2019, uploaded). This was developed by refining question content in patient focus groups, and then tested in a large survey. The results are presented in the attached publication. One of the main conclusions was that satisfaction was more dependent on communication and inter-personal contact between health care provider and patient, than in the actual pain management protocol. Furthermore, satisfaction with ED care was less than with specialised care.
(2) Direct feedback from patients enrolled in the SCAPE study, highlighting the value of one-to-one care from a nurse specialist in ED. This was published in a supplement to the SCAPE study report (uploaded elsewhere in this application)

21. Upload any documents that showcase your user testing

Elander_et_al-2019-British_Journal_of_Haematology (1).pdf

Filename: Elander_et_al-2019-British_Journal_of_Haematology (1).pdf **Size:** 160.0 kB

Section 5. REGULATIONS, STANDARDS, CERTIFICATIONS AND INTELLECTUAL PROPERTY

22. Do you know which regulations, standards and certifications apply to your innovation?

Yes, I know some of them

23. Which regulations, standards and certifications apply to your innovation?

Responses Selected:

Other, please specify...: NICE guideline: Sickle cell disease: Managing acute sickle pain in hospital 2012

24. Do you have a certification for UKCA / CE or In-vitro diagnostics?

Not yet

25. Upload all certification documents

Section 6. INTELLECTUAL PROPERTY

26. Do you have any patents for you innovation?

I do not have any patents, but believe I have freedom to operate

27. Do you have any other intellectual property for your innovation?

No

Section 7. REVENUE MODEL

28. What is the revenue model for your innovation?

Responses Selected:

Other, please specify: NHS funding through specialised commissioning or integrated care boards

29. Which NHS or social care organisation and department do you think would PAY FOR the innovation?

Be as specific as you can.

(100 word limit)

NHSE specialised commissioning, NHS integrated care networks

30. Which NHS or social care organisation and department do you think would BENEFIT FROM the innovation?

Be as specific as you can.

(100 word limit)

NHSE specialised commissioning, NHS Haemoglobinopathy co-ordinating centres, NHS Haemoglobinopathy Specialist centres, NHS hospitals, NHS Integrated care networks, primary care

31. Have you secured funding for the next stage of development?

No / Not revelant

31.2. Please explain why you do not need to secure funding.

(100 words)

Funding would need to be negotiated with NHS institutions listed above after pilot study results are evaluated

Section 8. COST AND SAVINGS

32. Do you know the cost of your innovation?

By cost, we mean the cost to the NHS or any care organisation that would implement your innovation.

Yes, I have a rough idea

33. What is the cost of your innovation?

Include the relevant metric such as a flat capital cost or cost per patient, cost per unit or cost per procedure. Include any costs associated with implementation and resources.

For example, £10 based on 500 units per site. £345 per procedure and a typical patient requires two procedures.

(100 word limit)

See attached costings
Two models are proposed: For 8am to 8pm 7 day per week service and 24 hours per day 7 days per week service. The service would be staffed by Band 6 nursing supported by a Band 7 nurse and supervised by a consultant haematologist (1 PA per week).
When not active in managing ED attendances, the specialist nurse would be supporting ward staff in managing in patients with acute pain.
We propose piloting in 3 or 4 haemoglobinopathy specialist centres

34. Roughly how many patients would be eligible for your innovation in the UK?

Up to 10,000 per year

35. What is the eligibility criteria for your innovation?

For example, users need to be over a certain age, or have a certain medical history or current health status.

Answer 'not relevant' if your innovation does not have any eligibility criteria.

(200 word limit)

Centre:
Medium/large haemoglobinopathy specialist centre (>1ED attendance per day).

Patients:
Registered with the SCD service
Attending ED with an acute pain episode
Personalised acute pain management protocol available on their electronic patient record

36. How many units of your innovation would you expect to sell in the UK per year?

(50 word limit)

At this stage we propose to pilot the implementation in up to 4 large/medium haemoglobinopathy specialist centres. There would be an option for patients managed in smaller local centres to travel to their specialist centre.

37. Approximately how long do you expect each unit of your innovation to be in use?

By this we mean the shelf life of the product, or the product's lifespan. This can include the lifespan of any components such as batteries.

(100 word limit)

The initial plan is for a one year project (See Gantt chart). Initial evaluation of pilots would be done using metrics of clinical efficacy, safety, patient satisfaction and health economics. At a later stage we would propose a randomised controlled trial comparing this with other care pathways (eg standard care in ED and with ambulatory care units)

38. What are the costs associated with the use of your innovation, compared to current practice in the UK?

My innovation costs more to purchase, but has greater benefits that will lead to overall cost savings

Section 9. DEPLOYMENT

39. Where have you deployed you innovation?

Provide the name of the organisation and the department, if possible.

(150 word limit)

Emergency department and acute medical wards, Royal London Hospital, Barts Health NHS Trust

40. What was the commercial basis for deployment?

For example, did you provide your innovation for free or was it purchased? Or was it part funded by yourself and the NHS area in which it's being deployed?

(400 word limit)

Funded as part of a research trial protocol, with contributions from Bart's Charity, Bart's Health NHS Trust and NIHR contingency funding.

41. How did the deployment of your innovation affect the organisation(s)?

For example, which job roles were affected and how was the care pathway redesigned?

(400 word limit)

Patients age 14 years, who were enrolled in the sickle cell disease service at Royal London Hospital, and met specific eligibility criteria were informed about the study and consented when attending for routine out patient care. If they developed an acute pain crisis they were instructed to phone the study administrator or nurse specialist, and to attend emergency department too receive care according to the study treatment protocol. On arrival in the ED, their care for the first 6 hours of the protocol was supervised by the study nurse specialist. This pathway differed from standard care, in two ways. Firstly, there is no routine phone contact prior to attending ED. Secondly, with standard care, initial management would be supervised by ED staff, and specialist haematology staff are generally involved at a later stage.

42. Does your team have the resources for scaling up to national deployment?

This includes having a team with the right combination of skills and knowledge.

No

43. Upload any relevant implementation planning documents

Gantt chart.xlsx

Filename: Gantt chart.xlsx **Size:** 10.3 kB

Costings.docx

Filename: Costings.docx **Size:** 15.6 kB

Acute sickle pain nurse activity flowsheet.pptx

Filename: Acute sickle pain nurse activity flowsheet.pptx **Size:** 52.5 kB

F. References

Completed - 26 Jul 2023

Please upload two reference letters in support of your application. One should be your line manager or senior individual from your organisation; the other should be from a healthcare provider/ commissioner site where your

innovation is currently in use (this does not need to be an NHS site).

HITC call Supportive Letter CRG

Filename: HITC_call_Supportive_Letter_CRG.pdf **Size:** 249.9 kB

LB PT suuport letter July 23

Filename: LB_PT_suuport_letter_July_23.doc **Size:** 239.1 kB

G. Additional Supporting Document (if needed)

Completed - 25 Jul 2023

If you have additional supporting information that helps to explain your innovation and the assessor to understand your proposal, please upload this here.

Please upload a maximum of one document.

This section is not compulsory and does not need be completed for the application to be submitted.

Patient testimonials from Telfer et al BJPain 2021

Filename: Patient_testimonials_from_Telfer__xLpzYsy.docx **Size:** 13.8 kB

H. Equal Opportunity Monitoring Form

Completed - 21 Jul 2023

Form is compulsory but applicants can indicate at the start of the form if they do not wish to complete it.

Equal Opp Monitoring Form

NB. Please can you ensure you set the site language to English (British) by clicking on your user name (top right hand corner on the menu bar), selecting My Account and updating default language settings to English (British).

The NIA aims to appoint exceptional individuals regardless of their age, disability, gender reassignment, marriage and civil partnership, pregnancy or maternity, race, religion or belief, sex or sexual orientation. The NIA is an equal opportunity Fellowship programme and is committed to recruiting Fellows that reflect the diverse communities we serve. To ensure that the programme is open and accessible to all and that our policies are fairly implemented and monitored, and for no other reason, would you please provide the information requested below.

The information you provide will:

• not be used as part of the selection process;

• not be seen by the interview panel;

• only be used by the NIA internal team for statistical purposes.

No information will be published which allows any individual to be identified.

The form should only take a few minutes to complete.

Please indicate by selecting an answer below if you will complete the Equal Opportunities Monitoring Form

I will complete the form

Age

55-64

Disability

You will be considered as having a disability for discrimination purposes if you fit the definition as given in the Equality Act 2010. In the Act, a disability is a 'physical or mental impairment which has a substantial and long term adverse effect on a person's ability to carry out normal day to day activities.' For these purposes, 'long term' is taken to mean the condition is likely to last longer than 12 months or likely to recur.

No, I do not have a disability

Ethnicity

Prefer not to say	✖
Asian or Asian British	(No response)
Black or Black British	(No response)
Mixed race	(No response)
White	British
Other Ethnic Group	(No response)

Religion or Belief

Christian

Gender Indentity

Man

Have you gone through any part of a process (including thoughts or actions) to change from the sex you were described as at birth to the gender you identify with, or do you intend to? (This could include changing your name, wearing different clothes taking hormones or having any gender reassignment surgery).

No

Sexual Orientation

Heterosexual / straight

Are you a parent or caretaker of children (under 18)?

Yes - secondary caregiver

Are you a caretaker of adults?

Yes - secondary caregiver

Do the adult(s) you care for have any of the following?

Problems related to old age

Permission to Use Data provided

The programme uses this information to review compliance with its policies on equal opportunity in relation to recruitment. We will use this data to inform our statistics on the representation of the categories of individual as shown above. We will treat all personal information in line with current data protection legislation and our data protection policy. For more information on how we use the information you have provided, please see our privacy notice for applicants which can be found **here**. In order for us to process this information and to comply with data protection legislation, we require your consent. You are not required to give your consent; you acknowledge that any consent given is freely given. Your NIA application is not dependent on your giving consent to our processing of this data. Including your signature below will signify your consent to our processing of this information. Once you have given consent, you may withdraw it at any time by contacting NIA@uclpartners.com.

I consent to the use of my data for monitoring purposes as per the statement above

King's College Hospital
NHS Foundation Trust

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24/07/2023

Professor Paul Telfer
Consultant Haematologist
Barts Health NHS Trust
Queen Mary University London
p.telfer@nhs.net

Dear Professor Telfer

Re: Health Inequalities Targeted Call (HITC): Sickle Cell Disease

As Chairperson for the Clinical Reference Group for Haemoglobin Disorders, I am writing to support your application to the HITC for evaluation of the role of Acute Sickle Pain Nurse Specialist for the management of acute sickle painful episodes in a hospital setting. You are acting as principal applicant on behalf of the National Sickle Cell Pain Advisory Group.

The pain group represents multiple stakeholders dedicated to improving management of acute sickle cell pain and has recognised that the quality of care and patient satisfaction with care in ED needs to be improved, and that the Acute Sickle Pain Nurse Specialist innovative role would be a potential means of achieving improvement.

I wish you success with your application

Yours sincerely,

Subarna Chakravorty

Dr Subarna Chakravorty MBBS PhD FRCP FRCPath MRCPCH
Consultant Paediatric Haematologist

cc
Zoe Hamilton
National Programme of Care Manager – Blood and Infection
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NHS England
zoe.hamilton6@nhs.net

Article

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A non-injected opioid analgesia protocol for acute pain crisis in adolescents and adults with sickle cell disease

Paul Telfer[1,2], Jonathan Bestwick[3], James Elander[4], Arlene Osias[2], Nosheen Khalid[5], Imogen Skene[6], Ruben Nzouakou[2], Joanne Challands[7], Filipa Barroso[2] and Banu Kaya[2]

Abstract

Initial management of the acute pain crisis (APC) of sickle cell disease (SCD) is often unsatisfactory, and might be improved by developing a standardised analgesia protocol. Here, we report the first stages in developing a standard oral protocol for adolescents and adults. Initially, we performed a dose finding study to determine the maximal tolerated dose of sublingual fentanyl (MTD SLF) given on arrival in the acute care facility, when combined with repeated doses of oral oxycodone. We used a dose escalation algorithm with two dosing ranges based on patient's weight (<50 kg or >50 kg). We also made a preliminary evaluation of the safety and efficacy of the protocol. The study took place in a large tertiary centre in London, UK. Ninety patients in the age range 14–60 years were pre-consented and 31 treatment episodes were evaluated. The first 21 episodes constituted the dose escalation study, establishing the MTD SLF at 600 mcg (>50 kg) or 400 mcg (<50 kg). Further evaluation of the protocol indicated no evidence of severe opioid toxicity, nor increased incidence of acute chest syndrome (ACS). Between 0 and 6 hours, the overall gradient of reduction of visual analogue pain score (visual analogue scale (VAS)) was 0.32 centimetres (cm) per hour (95% confidence interval (CI) = 0.20 to 0.44, $p < 0.001$). For episodes on MTD SLF, there was median (interquartile range (IQR)) reduction in VAS score of 2.8 cm (0–4.2) and 59% had at least a 2.6-cm reduction. These results are supportive of further evaluation of this protocol for acute analgesia of APC in a hospital setting and potentially for supervised home management.

Keywords

Sickle, crisis, pain, opioid, VOC, analgesia

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Introduction

The acute pain crisis (APC) is the commonest acute complication of sickle cell disease (SCD).[1] Severe episodes are distressing, disruptive to normal activity, associated with life-threatening complications such as acute chest syndrome (ACS), and may predispose to chronic pain.[2] Initial management in the emergency department (ED) or other acute care setting requires rapid assessment and administration of first dose of analgesia, usually opioid, within 30–60 minutes.[3–5] Afterwards, repeated doses of analgesia are generally required, together with mandatory monitoring in order to ensure adequacy of analgesia, to anticipate additional complications of APC and to avoid opioid toxicity.[3,5,6] There is no standard analgesia protocol for paediatric, adolescent or adult patients and controversy remains around a number of aspects of the treatment pathway including choice of opioid, timing and route of administration, and differences in practice between children, adolescents and adults. This prompted the National Heart Lung and Blood Institute (NHLBI) panel in the United States[3,7] and the National Institute of Clinical and Health Care Excellence (NICE) in the United Kingdom[4] to recommend studies to determine optimal management of APC.

Morphine, the most commonly used opioid,[8] is a mu receptor agonist, metabolised mainly through glucuronidation by the enzyme UGT2B7. The resulting metabolites include morphine-6-glucuronide (M6G), which is pharmacologically active and has been associated with an increased risk of ACS.[9] Oxycodone and fentanyl are strong opioids which differ from morphine in pharmacokinetics, undergoing extensive first-phase metabolism via CYP2D6 and CYP3A4 pathways, enzymes which are potentially activated or inhibited by a range of drugs that could affect the therapeutic response.[10] Oral oxycodone is commonly used for home management of pain in the United States,[11] but might be a suitable alternative to morphine for management of acute sickle cell pain in patients who have not been heavily exposed to strong opioids.

With regard to the route of administration, the intravenous route is generally accepted as the gold standard, but there are a number of considerations which justify efforts to develop non-intravenous opioid protocols in both paediatric and adult SCD populations. First, delays in administration of analgesia often occur because of poor venous access. Second, there is evidence from the addiction literature both from animal studies and human observation studies, that rapid and frequent elevations in plasma and brain drug levels during intravenous administration are more likely to induce tolerance and dependency.[12] Although evidence for this effect in patients with SCD is lacking, we believe that there is cause for concern about adverse effects associated with repeated doses of intravenous opioids given over a prolonged period in this patient group. Studies in children which show that a standardised oral-based opioid protocol can be effective and safe[13,14] suggest that this kind of protocol could also be evaluated in adolescents and adults.

Opioid drugs can be rapidly absorbed through the oral and nasal mucosa, leading to a rapid rise in plasma drug levels.[15] For instance, the onset of action for sublingual fentanyl is 8–10 minutes and peak effect at 40–60 minutes.[16] The transmucosal route of administration could potentially enable rapid action of the first dose of opioid analgesia, avoiding delays entailed with intravenous administration. By restricting transmucosal opioid to the first dose only, the potential risks associated with sharp elevations in plasma and brain opioid levels may be mitigated. Intranasal and buccal fentanyl have been used to manage acute sickle pain in children and adults, but it is not clear how best to incorporate additional rapid-acting opioid analgesia into a standard protocol for acute pain.[6,17,18] We have previously shown that intranasal diamorphine (IND) given as a single acute dose in combination with a pre-scheduled protocol of oral morphine can provide effective analgesia in children and potentially reduce the time to first analgesia compared to intravenous opioid.[14,19] Some problems with use of IND were identified. First, 35% of children found IND uncomfortable, particularly adolescents, who are administered a higher concentration of diamorphine solution because of their greater weight. Second, diamorphine is not available in some health care systems and uptake might be limited by perceived association with drug dependency.

The overarching aim of our programme of work is to develop a standard oral-based analgesia protocol, suitable for rapid administration in the ED. In this study, we assessed the maximal safe dose of sublingual fentanyl (Abstral®) given on arrival in the acute health care facility, when combined with a programmed dosing schedule of oral oxycodone. Oxycodone was chosen in this protocol building on our previous experience of using oxycodone as a replacement opioid in adolescent and adult patients treated in our institution who had adverse effects, or poor pain control with morphine. The study also aimed to obtain preliminary data on efficacy and safety which could be used to design a follow-up randomised controlled trial comparing this protocol with standard analgesia.

Methods

Protocol development

Our standard institutional analgesia protocols are based on short-acting oral morphine for breakthrough and controlled-release morphine for background analgesia. Some adults, particularly those with more

severe or frequent hospitalisations, are treated with subcutaneous injections combined with controlled-release oral long-acting opioid for background analgesia. The study was part of a long-term programme of work in our service to improve pain management and patient experience, involving consultation with patients, families and the wider SCD multi-disciplinary team.[14,19–21] We had previously developed a protocol for children to ensure rapid onset of analgesia and sustained analgesia without using injected opioids. We used a single dose of transmucosal opioid (IND) on first arrival in ED, to obtain rapid increase in plasma drug concentration and rapid analgesic effect. The pharmacokinetics of oral short-acting opioid are slower than for transmucosal, but we predicted that if the oral short-acting opioid is administered simultaneously with transmucosal, drug levels should reach analgesic levels simultaneously with the decrease in drug levels of transmucosal opioid.[15] In this way, we aimed to ensure sustained opioid drug levels and analgesia effect during the first few hours of pain management. In this study, we modified this analgesia protocol for use in adolescents and adults by replacing IND with sublingual fentanyl (SLF; Abstral®, Kyowa Kirin). For breakthrough analgesia, short-acting oral morphine was replaced with oral short-acting oxycodone (OxyNorm®, Mundipharma), and for background analgesia, controlled-release morphine was replaced with controlled-release oxycodone (OxyContin®, Mundipharma). The protocol is shown in Figure 1.

Consent, inclusion and exclusion criteria

Patients were consented in the out-patient setting and consent confirmed on presentation with APC. Inclusion and exclusion criteria are shown in Table 1. We excluded those weighing less than 35 kg and those who were taking strong opioids (as defined in the NICE guideline)[4] as a regular daily analgesic prescription at home. There was no limit to the annual rate of admissions with APC prior to participation in the study.

Study procedures

In the event of APC requiring treatment in hospital, the patient or parent/guardian was asked to phone the trial centre to inform of their intention of attending. Children were directed to the paediatric ED, adults (age >16 years) either to the adult ED or, if there was a bed available, to the haematology day unit (HDU). The trial was implemented with the assistance of a dedicated nurse and a trial manager. Paediatric and emergency medicine clinical research teams contributed to delivery of the trial in their respective areas. Monitoring and treatment over the first 6 hours were done by the trial nurse, while management after 6 hours was undertaken by standard care clinical and nursing staff. The intention was to continue oral analgesia according to the trial protocol, after the first 6 hours of treatment on the protocol, but there was an option to switch to alternative oral opioid or injected opioid using institutional protocols. Ibuprofen and paracetamol at standard recommended dosage were routinely prescribed and administered as additional analgesic medication.

Part 1: determination of MTD SLF

Sequential dosing of groups of three episodes was undertaken using a 'group up-and-down' algorithm,[22] with two dose options depending on the patient's weight (<50 kg or >50 kg). The dose of short-acting oxycodone was fixed at 10 mg (<50 kg) and 15 mg (>50 kg). The range of doses of fentanyl is shown in Table 2. For safety monitoring, we used indicators adapted from the National Early Warning Score (NEWS, https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2). These consisted of respiratory rate (RR) and sedation according to the AVPU scale (Alert, responds to Verbal instructions, Painful stimuli or Unresponsive). The lowest anticipated effective dose was initially used and after three episodes had been completed, the trial safety monitoring committee (TSMC) assessed safety at time points t = 0, 30 minutes, 1 hour and hourly up to 6 hours. A patient was classified as intolerant if the AVPU score was P or U, or if RR was below 8 per minute at any of these time points. If all patients were tolerant, the dose was increased by one iteration. If one or more patients were intolerant, the dose was reduced by one increment. The MTD was to be the most commonly used dose after 21 adjudicated episodes.

Part 2: further data collection using MTD SLF

After completion of the dose finding study, we aimed to obtain further data on safety and efficacy using MTD SLF to determine suitable end points for a controlled trial. Although not formally powered, the protocol envisaged a total of 30 episodes at MTD (including episodes treated during both Parts 1 and 2), but the study was actually terminated after a total of 22 episodes at MTD SLF, due to funding constraints.

Patient-reported outcomes

Patient satisfaction was elicited by verbal and written feedback as part of the protocol-specified follow-up 28 days after discharge.

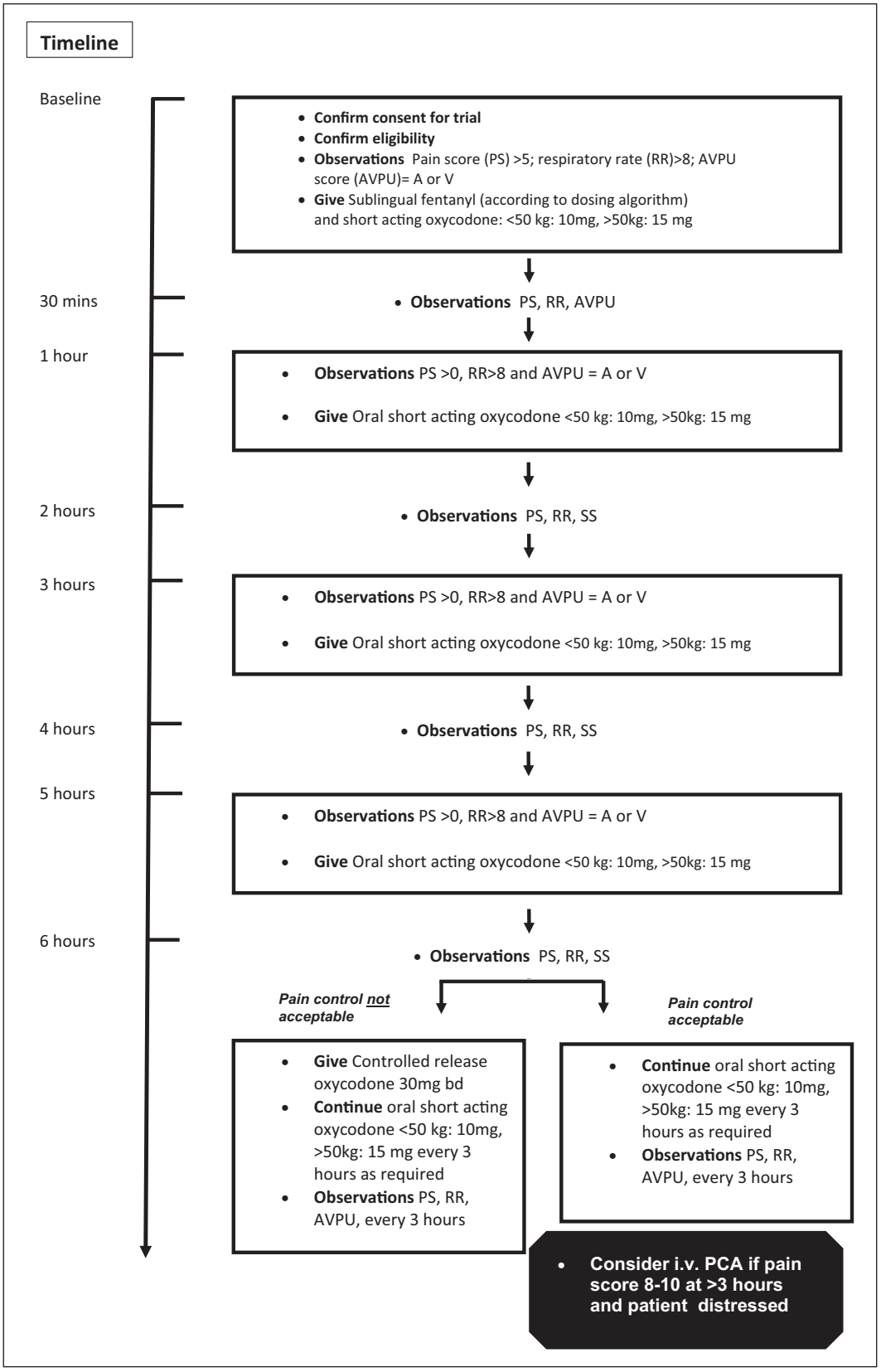

Figure 1. Treatment and observation flow chart.
PS: pain score, RR: respiratory rate, A: alert, V: responds to verbal commands, P: responds to painful stimuli, U: unresponsive, PCA: patient-controlled analgesia.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
At consent
1. Diagnosis of SCD (any genotype) 2. Aged 14–60 years
At confirmation of consent
Points 1–2 as above plus 1. VOC requiring hospital treatment 2. Pain score 5 or more on verbal 1–10 scale 3. Part 1: no more than one previous pain crisis treated with trial protocol; Part 2: no more than two previous pain crises treated with trial protocol
Exclusion criteria
At consent
1. Weight <35 kg 2. History of allergic reaction to fentanyl or oxycodone or their excipients 3. Severe hepatic or renal impairment 4. Regular daily home medication with strong opioids 5. Administration of CYP3A4 inhibitor 6. Concurrent administration of Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or monoamine oxidase inhibitor (MAOI) within previous 2 weeks 7. Documented history of clinically significant brain tumour 8. History of severe symptomatic chronic obstructive airways disease or chronic asthma 9. History of pulmonary hypertension 10. Chronic constipation 11. Pregnant or breastfeeding 12. Unable to understand spoken or written English
At time of confirmation of consent
Points 1–12 as above plus: 1. Administration of strong opioid after arrival in acute care facility (ED or HDU) prior to enrolment in SCAPE protocol 2. Respiratory rate >28/min or <8/min 3. AVPU score = P or U 4. Blood pressure <80 systolic 5. Pulse rate <50/min 6. Uncontrollable vomiting 7. Hypovolaemia 8. Acute abdominal complication requiring surgical intervention 9. Paralytic ileus 10. Delayed gastric emptying 11. Clinical suspicion of stroke 12. Documented history of head injury 13. Raised intracranial pressure 14. Fulminant priapism in men 15. Ingestion of excessive alcohol within 12 hours of study entry 16. Ingestion of CNS depressant other than medication to treat VOC within 12 hours of study entry

SCD: sickle cell disease; HDU: haematology day unit; ED: emergency department; AVPU: Alert, responds to Verbal instructions, Painful stimuli or Unresponsive; CNS: central nervous system.

Safety monitoring and adverse event reporting

The main safety parameters were RR and sedation score. These were evaluated systematically for the first 6 hours after administration of study medication. After 6 hours, safety parameters were evaluated 3-hourly by the care team according to standard institutional protocols and these were recorded on standard institutional observations charts, reviewed by the trial team over time period 6–24 hours, and daily thereafter until discharge from hospital. Other opioid adverse effects

Table 2. Dosage algorithm for maximal tolerated dose (MTD) of sublingual fentanyl.

Patient weight	Dosage iteration				
	–1	Starting	+1	+2	+3
30–50 kg	100 mcg	100 mcg	200 mcg	300 mcg	400 mcg
>50 kg	100 mcg	200 mcg	300 mcg	400 mcg	600 mcg

(nausea and vomiting, pruritis, constipation and urinary retention) were monitored at baseline, 3 and 6 hours and then averaged daily until discharge from hospital, and graded on a 0–4 scale based on a published terminology of categories (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Definitions of severe adverse events were specified in the protocol to take account of the acute nature of APC and likely admission to hospital. These included abnormally prolonged hospital stay (more than 14 days) and potentially life-threatening complication of SCD including acute stroke, acute complication requiring exchange transfusion or admission to intensive care unit.

Funding and trial authorisations

The trial was funded by a grant from the Barts Charity (reference no. 1704), the National Institute for Health Research North Thames Clinical Research Network Divisional Contingency Funding, and unrestricted grants from Kyowa Kirin and Napp Pharmaceuticals. It was registered under the European Directory of Clinical Trials with reference number 2013-004161-14, and sponsored by Barts Health NHS Trust and Queen Mary University of London. Approvals for the initial protocol and subsequent amendments were obtained from the London City and East Research Ethics Committee (reference no. 14/LO/0165), the UK Medicines and Health Products Regulatory Agency (protocol no. 008414) and the National Health Research Authority. Details of protocol amendments during the study are given in Supplementary Appendix 1. The study was adopted by the National Institute for Health Research (NIHR) Clinical Research Network trials portfolio and conducted with the assistance of Pediatric and Emergency Medicines research teams at our institution.

Statistical analysis

MTD of SLF administered was considered the primary end point. A number of protocol-defined efficacy and safety end points were evaluated for potential use in a subsequent controlled trial. These were principally focussed on the first 6 hours of treatment, but data were also collected beyond 6 hours for analysis of overall efficacy and safety during admission and after discharge. Visual analogue scale (VAS) pain score between baseline and 6 hours was analysed using time series regression analysis. Predictor factors were MTD versus not MTD, sex, paediatric versus adult and weight >50 kg or <50 kg.

Results

Participants

Ninety patients were consented. Overall, 31 treatment episodes in 23 patients were evaluated, including 21 episodes in 19 patients in Part 1 for determination of MDT SLF and a further 10 episodes in seven patients at MTD SLF in Part 2. Sixty-three episodes in 34 consented patients were not evaluated. Forty (63.5%) of these episodes were treated outside of normal working hours of the trial team and 23 (36.5%) did not meet inclusion criteria. Reasons for not meeting inclusion criteria included presentation for causes unrelated to pain, administration of alternative opioid analgesia in ED, taking excluded additional medication and previously treated more than permitted number of times in study. Excluded episodes were treated with standard institutional analgesia protocols. Altogether, including episodes in Parts 1 and 2, 22 treatment episodes in 14 patients were evaluated at MTD SLF. The consort diagram for the study is shown in Figure 2, the baseline clinical features of study participants are shown in Table 3, and the clinical features of the episodes are shown in Table 4. Seven (30%) were under 18 years of age, four (17%) were under 50 kg in weight and as per protocol received the lower dose of SLF and oxycodone. Prior to arrival in hospital, opioids were administered for 22/31 (71%) of episodes. This includes moderate and strong opioids taken at home and opioid administered in the ambulance in those who required ambulance transport. Ten episodes were initially treated in our HDU and 21 in ED.

Determination of maximal tolerated dose of SLF

SLF dose was increased sequentially up to the maximum specified on the algorithm (600 mcg for >50 kg or 400 mcg for <50 kg). This being the most frequently

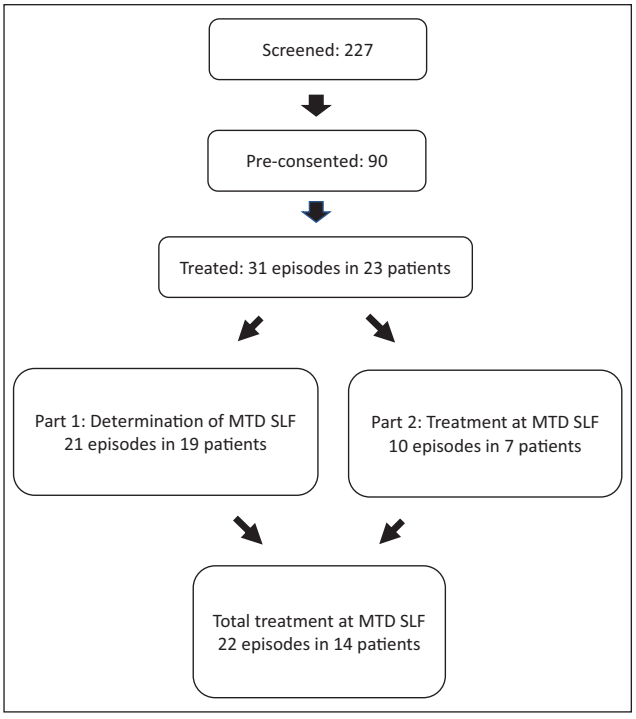

Figure 2. Consort study diagram.

used dose, it met the criteria for MTD SLF. During the first 6 hours of treatment, there was no evidence of respiratory depression (RR <8/min) and no significant difference in RR at different dose increments. There was one episode associated with sedation (AVPU score of P in episode 11), but this episode was a presentation with severe ACS; sedation occurred after switching to intravenous opioid analgesia and was associated with hypoxaemia due to acute pulmonary sickling. This was reversed with urgent exchange transfusion instituted within 6 hours of triage.

Dosing of short-acting oxycodone

The analgesia protocol included pre-specified doses of short-acting oxycodone during the first 6 hours. All patients received the initial oxycodone dose simultaneously with SLF, but at subsequent time points, scheduled doses were not given in some cases. The main reasons for withholding doses were physician decision that the patient was becoming too drowsy (AVPU score of 'V', responds to verbal commands), and particularly towards the end of the 6-hour study period because pain had settled and the patient was considered ready for discharge.

Efficacy

Median verbal pain score on presentation was 7 (range 5–10) (Table 3). After confirmation of consent and trial enrolment, pain score was re-evaluated by VAS prior to first treatment (t = 0). Median VAS score was 6.5 cm (range = 2.7–10). This difference in pain reported verbally compared to VAS may relate to variations in patient behaviour in reporting verbally compared to VAS, or to delayed effects of analgesia administered at home or in transit, prior to treatment in the study.

Thereafter, the gradient of reduction of VAS pain score was 0.32 cm per hour (95% confidence interval (CI) = 0.20 to 0.44, $p < 0.001$). There was no significant difference in gradient between patients on MDT SLF and sub-MDT SLF, between males and females, and between those in the highest and lowest quartiles for age and weight. Further efficacy end points are detailed in Table 5. For MTD SLF, median reduction (interquartile range (IQR)) in VAS score from t = 0 to 6 hours was 2.8 cm (0–4.15) and 59% had a reduction of at least 2.6 cm. Three episodes in two patients required intravenous opioid via patient-controlled analgesia (PCA). In one case, change in route of opioid administration was within the first 6 hours and was used to help with management of ACS rather than for uncontrolled pain. For the five patients whose standard treatment was parenteral opioids, efficacy responses were similar to those whose standard treatment was oral opioids (Supplemental Table 1).

Readmission included ED attendances and hospital admissions. There were a total of 13 readmissions (42% of episodes) of which 6 were within 7 days (19%) and 7 within 14 days (23%). Duration of hospital stay and readmission rate were lower in patients on MTD SLF compared with sub-MTD SLF, but these differences were non-significant (Table 5).

Safety

Opioid adverse effects observed during the first 6 hours of treatment are illustrated in Figure 3. These were generally mild or moderate. There were no cases of RR below 11 per minute, which would be contributed to a higher risk score in the NEWS system. At MTD, there was one case of severe sedation (P) in a patient who presented to ED with evidence of ACS prior to dosing. MTD was also associated with more cases of mild sedation (V) on the AVPU scale. The majority of participants reported pruritis grade 1 at doses of 300/200 mcg and above. Grade 1 nausea was also more common at MTD SLF. There was no difference in symptoms of dizziness and one case of self-limiting urinary retention at the highest dose.

Serious adverse events (SAEs) were observed in seven episodes in six patients. Four SAEs were due to prolonged hospitalisation, and in these cases, there were no additional complications of SCD. There

Table 3. Clinical features of study patients.

	Sub-MTD SLF 9 patients	MTD SLF 14 patients	Total 23 patients
Demographics			
Age, years, median (range)	19 (16–38)	21 (12–41)	21 (12–41)
Age <18 years, number (%)	3 (33)	4 (29)	7 (30)
Female, number (%)	3 (33)	7 (50)	10 (44)
Weight <50 kg, number (%)	1 (11)	3 (21)	4 (17)
Genotype HbSS, number (%)	9 (100)	13 (93)[a]	22 (96)[a]
Treatment			
Hydroxycarbamide, number (%)	2 (22)	7 (50)	9 (39)
Regular transfusion, number (%)	2 (22)	2 (14)	4 (17)
Acute pain history			
Annual admissions, median (range)[b]	3 (0–14)	4 (0–16)	4 (0–16)
Annual home-managed, median (range)[c]	32 (4–96)	7 (0–30)	24 (0–120)
Home opioid usage[d]			
Moderate strength opioid[e]			
Number (%)	7 (78)	10 (71)	17 (71)
Median days per month (range)	8 (0–14)	1 (0–14)	1 (0–14)
Strong opioid[e]			
Number (%)	4 (44)	5 (36)	9 (38)
Median days per month (range)	0 (0–7)	0 (0–10)	0 (0–10)
Usual hospital analgesia protocol, number (%)			
Intranasal diamorphine, oral short-acting morphine and controlled-release morphine	0 (0)	1 (7)	1 (4.3)
Fentanyl lozenge, oral short-acting morphine and controlled-release morphine	7 (78)	8 (57)	15 (65)
Subcutaneous morphine and controlled-release morphine	2 (22)	3 (21)	5 (21)
Subcutaneous oxycodone and controlled-release oxycodone	0 (0)	1 (7)	1 (4)

MTD SLF: maximal tolerated dose of sublingual fentanyl.
[a]One patient was HbSC.
[b]Averaged over 24 months prior to consent.
[c]Calculated from self-report over previous 3 months at consent.
[d]Self-report over previous month, at consent.
[e]Moderate strength opioids include codeine, dihydrocodeine and tramadol, and strong opioids include morphine formulations and oxycodone.

were three cases of ACS in two patients. The first presented with symptoms of ACS prior to receiving study medication. This patient underwent emergency exchange transfusion and was switched from study analgesia protocol to intravenous fentanyl PCA at 3 hours, making a rapid recovery. A second patient presented with uncomplicated pain episode and was treated with the study protocol and made a rapid recovery. This patient represented on two further occasions over the next 2 weeks, on the second occasion had a rapid deterioration in respiratory function and died. During the second and third admissions, the patient was treated with a standard institution analgesia protocol. The enquiry into this tragic fatal event identified delay in recognising ACS and instituting emergency exchange transfusion. Since the event occurred 10 days after administration of a single dose of SLF, it was not considered related to study medication or procedures.

Patients dosed on more than one occasion

The protocol allowed up to two treatment episodes per patient in Part 1 and a total of three treatment episodes per patient in total. During the study, five patients were treated more than once (three patients treated three times and two patients treated twice). All 13 of these treatment episodes were at MTD SLF. There was marked variability in efficacy when episodes within an individual patient were compared. None of the patients treated for repeated episodes were observed to have significant opioid adverse

Table 4. Clinical features of treated acute pain crises.

	Sub-MTD SLF (n = 9)	MTD SLF (n = 22)	Total (n = 31)
Site of pain			
Extremities[a]	6 (67)	16 (73)	22 (71)
Back	4 (44)	13 (59)	17 (55)
Chest	3 (33)	7 (32)	10 (33)
Head	1 (11)	3 (14)	4 (13)
Abdo	0 (0)	5 (23)	5 (16)
Analgesia taken at home prior to attending hospital			
Paracetamol	5 (56)	15 (68)	20 (65)
NSAID	5 (56)	9 (41)	14 (45)
Moderate strength opioid[b]	3 (33)	14 (67)	17 (55)
Strong opioid[c]	3 (33)	3 (14)	6 (19)
Mode of transportation to hospital			
Ambulance	5 (56)	3 (14)	8 (25.8)
Car	2 (22)	8 (36)	10 (32)
Public transport	2 (22)	11 (50)	13 (423)
Physical signs at presentation			
Jaundice	8 (89)	21 (96)	29 (94)
Pallor	2 (22)	18 (82)	20 (65)
Respiratory signs	0 (0)	2 (9)	2 (6)
Abdominal signs	0 (0)	3 (14)	3 (10)
Priapism	0 (0)	0 (0)	0 (0)
Neurological signs	0 (0)	1 (5)	1 (3)
Other[d]	1 (11)	3 (14)	4 (13)
Vital signs at presentation			
	Mean (range)	Mean (range)	Mean (range)
Verbal pain score (1–10)	7 (6–9)	8 (5–10)	7 (5–10)
Respiratory rate (per min)	17 (12–19)	20 (14–28)	19 (12–28)
Sedation (AVPU) score[e]	A in all cases	A in all cases	A in all cases
Pulse rate (per minute)	82 (60–111)	86 (67–129)	85 (60–129)
Oxygen saturation (%)	96 (87–100)	96 (92–100)	96 (87–100)
Temperature (°C)	36.4 (35.1–37.6)	37 (36.1–38.8)	37 (35.1–38.8)
Blood pressure (systolic)	116 (97–140)	124 (94–153)	122 (94–153)
Blood pressure (diastolic)	63 (52–77)	68 (49–93)	66 (49–93)

MTD SLF: maximal tolerated dose sublingual fentanyl; NSAID: non-steroidal anti-inflammatory.
Figures in parentheses are the percentages.
[a]Extremities includes L or R arm, L or R leg.
[b]Moderate strength opioid: codeine phosphate, dihydrocodeine and tramadol.
[c]Strong opioid: oral short-acting or controlled-release morphine and oral short-acting or controlled-release oxycodone.
[d]Tender areas on extremities in four cases.
[e]A: alert; V: responds to verbal commands; P: responds to painful stimuli; U: unresponsive.

events (Supplemental Table 1). One patient experienced ACS, related to two of the three treatment episodes.

Participant satisfaction

Feedback on the standard protocol questionnaire was obtained 28 days after discharge for 25 episodes in 19 patients. Feedback was not available for six episodes, because patient was uncontactable (5) or patient deceased (1). In 23 of 25 (92%) episodes surveyed, the patient stated they would like to receive the protocol again. Additional written feedback was received which was highly supportive of the protocol (Supplementary Appendix 2).

Discussion

We have shown that a single dose of SLF at 400 mcg (<50 kg) or 600 mcg (>60 kg) when combined with a pre-scheduled dosing of oral oxycodone is safe for adolescents and adults and can be used for initial management of APC in the acute care setting.

There is an evidence gap in management of APC which has been acknowledged by the NHLBI in the United States[7] and by the NICE in the United Kingdom.[4] Our protocol addresses some of the areas of uncertainty about optimal care, including alternative routes of opioid administration, and treatment in the adolescent and young adult age group.

Table 5. Efficacy end points.

End point	Sub-MTD SLF 9 episodes	MTD SLF 22 episodes	p-value
Reduction in VAS score from baseline to 6 hours, median (IQR)	2.4 (0.4–5.6)	2.8 (0.0–4.1)	NS
Reduction >1.3 cm in VAS at 6 hours, number (%)	5 (56)	15 (68)	NS
Reduction >2.6 cm in VAS at 6 hours, number (%)	4 (44)	14 (59)	NS
VAS score <5 by 6 hours, number (%)	5 (56)	15 (68)	NS
Discharged from ED/HDU by 6 hours, number (%)	3 (33)	9 (40)	NS
Opioid used during first 6 hours, average oral morphine equivalent in mg/kg (range)	1.1 (0.6–2.0)	1.1 (0.4–1.6)	NS
Time to first dose of analgesia, average minutes (range)	46 (21–76)	53 (27–93)	NS
Duration of hospital stay, days (range)	6.8 (0–28)	2.4 (0–10)	NS
Opioid used during first 24 hours, average oral morphine equivalent in mg/kg (range)	2.1 (0.6–5.2)	2.2 (0.4–7.8)	NS
Opioid used during episode, average oral morphine equivalent in mg/kg (range)	10.8 (0.6–32.6)	13.7 (0.4–189.1)	NS
Conversion to injected opioid, number (%)	2 (22)	4 (10)	NS
Readmission, number (%)	5 (56)	8 (36)	NS

MDT SLF: maximal tolerated dose sublingual fentanyl; IQR: interquartile range; ED: emergency department; HDU: haematology day unit; NS: not significant.

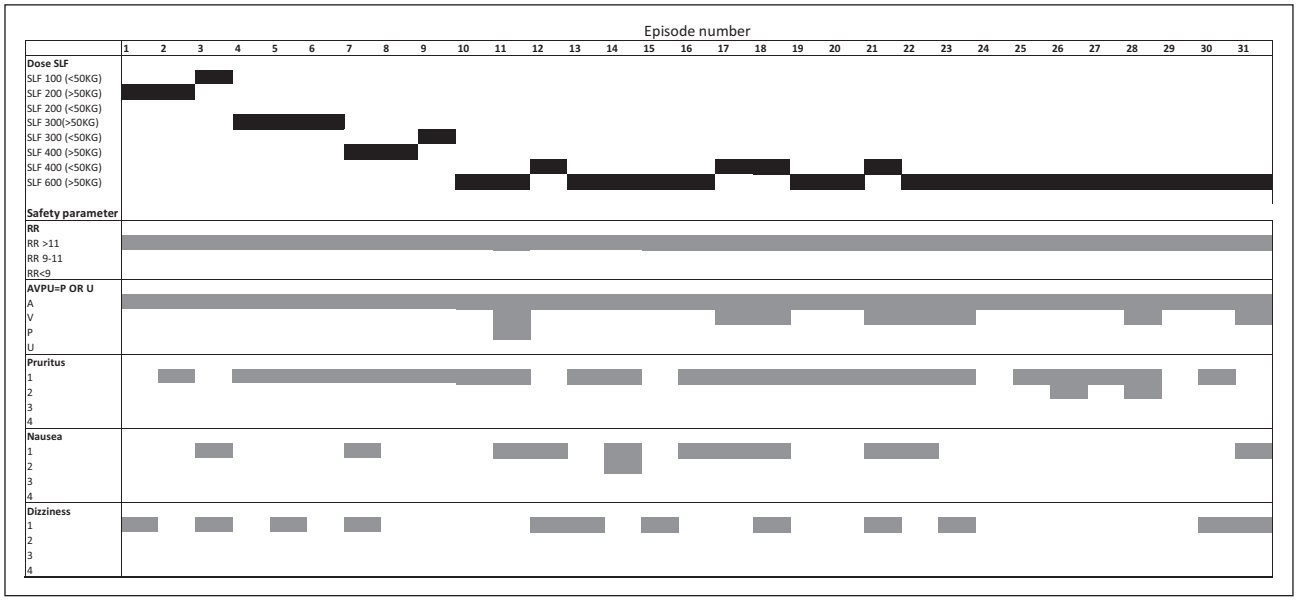

Figure 3. Sublingual fentanyl dosing and opioid adverse events (during the first 6 hours of monitoring) are shown diagrammatically for each treatment episode. MTD episodes are episodes 10–31. In the top section, the black bar represents the dose of SFL given for the treatment episode. In the second and third sections, the most severe degree of respiratory depression and sedation, and in the lower sections, most severe grades of pruritis, nausea and dizziness for each episode are shown as grey bars.
SLF: sublingual fentanyl (dose in micrograms); RR: respiratory rate; A: alert; V: responds to verbal commands; P: responds to painful stimuli; U: unresponsive.

With regard to safety, patients were carefully evaluated over the first 6 hours of observation. There was no evidence of significant over-sedation or respiratory depression, the primary concerns with use of strong opioids. Reporting of other adverse effects was as expected, with mild pruritis, nausea and dizziness frequently reported, mostly at mild severity. ACS was reported in three episodes (9.6%), but none were considered causally related to the analgesia protocol. Rates of ACS in previous studies have been variable, ranging from 3% to 57%,[9,23–26] and our results do not suggest a higher rate of ACS with oral opiates. We suggest that the risk of ACS associated

with oral opioids, as reported in a study of oral versus intravenous morphine, is probably overstated.[9]

Although not formally designed to evaluate efficacy, the data suggest similar efficacy to other analgesia protocols used in SCD. Changes in the VAS pain score over the first 6 hours of treatment or until decision on disposition in ED have previously been evaluated,[27–29] leading to the suggestion that a change in pain intensity between 1.3 and 2.6 cm on a 10-cm VAS scale would be considered clinically significant.[30] For episodes treated with MTD SLF in this study, the data suggest a clinically significant reduction in pain, with median reduction of 2.8 cm and 59% of episodes demonstrating at least a 2.6-cm reduction in VAS at the 6-hour time point. In comparable trials of analgesia, the mean reduction was in the range of 2–4 cm.[27–29] We observed that most of the efficacy measures evaluated showed greater efficacy of MTD SFL over sub-MTD SLF, and this supports a policy of administering the highest safe dose of rapid-acting opioid analgesia.

In our experience, some patients continue to experience pain in the first 1–2 weeks after discharge, and in some cases require readmission to hospital. ED reattendance and hospital readmission rates were high, but similar to recent studies of patients treated with intravenous opioids in the United States of 35–50%.[27,31] It is not yet clear how the readmission rate relates to efficacy and acceptability of the study analgesia and we plan to investigate this end point in a randomised controlled study. The evaluation at 28 days was intended to enable full recovery from the episode and withdrawal of analgesic medications which could interfere with judgement of satisfaction. In general, patients had a good recollection of their experience during treatment after the 28-day interval. Participant feedback was generally very positive, and a high proportion of those surveyed wished to be treated again with the same protocol. In an ancillary study where a group of our service users participated in developing a questionnaire to evaluate patient satisfaction with pain management in hospital, we found that satisfaction was not primarily determined by the analgesia protocol, but by the quality of communication, and attitudes of staff in ED and medical wards.[20] The benefit of one-to-one nursing care given by the trial nurse during the first 6 hours of the protocol was particularly notable in this study. This suggests that continued communication, reassurance and support sustained over the first 6 hours of management in ED and, if admitted, on transfer to the hospital ward were highly valued and contributed to the overall patient-reported outcome. Resources should be directed to this aspect of care.

The protocol was developed following our experience with use of combined IND and short-acting oral morphine in children. We demonstrated that the first dose of IND could usually be delivered by ED staff well within the recommended time limit.[14,19] In this study, we did not attempt to address timeliness of this first dose, recognising that in the trial setting, delays occur in assessing eligibility, obtaining consent and administering an investigational medicinal product. In order to confirm a satisfactory performance with regard to time to first analgesia, the protocol would need to be formally implemented with training of acute care staff, and further evaluation undertaken by auditing outcomes during routine care.

In a previous study with oral opioid protocols, we found that dosing needed to be proactive in the first 6 hours and scheduled doses given even if pain is at the mild end of the scale (VAS score 1–3), to avoid relapse.[14] In this study, some patients became drowsy (AVPU score of 'V') with repeated doses of oral oxycodone, and some scheduled doses were omitted on the decision of the trial physician. We would therefore suggest a revision to the protocol with scheduled dose of oxycodone omitted if VAS pain score is <3.

Patients who used strong opioids on a daily basis were excluded from the study, and only 38% of patients treated in this study used strong opioids episodically for home management of acute pain, compared to 75% in some adult studies in the United States.[11,32] The protocol is unlikely to be successful for patients who are already heavily exposed to opioids, and may not be acceptable to some patients who are already established on intravenous protocols for pain management in hospital. We suggest that a comparative trial would be of most value in adolescent and young adult populations who are not frequent attenders to hospital and are not yet heavily exposed to opioids.

In conclusion, these results provide evidence that the study protocol is safe, acceptable and potentially effective for initial pain management of APC in adolescents and adults. Use of SLF on arrival in ED, combined with pre-scheduled oral opioid, could reduce time to first analgesia as well as preventing short- and long-term complications associated with repeated use of intravenous opioids. We suggest that the protocol should be further evaluated in different health care settings, including supervised treatment at home, as well as being formally compared to protocols based on injected opioids.

Conflict of interests

PT has received unrestricted grants from Kyowa Kirin and Napp Pharmaceuticals to undertake the study.

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Supplemental material

Supplemental material for this article is available online.

References

1. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. *New Engl J Med* 1991; 325: 11–16.
2. Telfer P and Kaya B. Optimizing the care model for an uncomplicated acute pain episode in sickle cell disease. *Hematology Am Soc Hematol Educ Program* 2017; 2017: 525–533.
3. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014; 312: 1033–1048.
4. Gillis VL, Senthinathan A, Dzingina M, et al. Management of an acute painful sickle cell episode in hospital: summary of NICE guidance. *BMJ* 2012; 344: e4063.
5. Brandow AM, Carroll CP, Creary S, et al. American society of hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv* 2020; 4: 2656–2701.
6. Akinsola B, Hagbom R, Zmitrovich A, et al. Impact of intranasal fentanyl in nurse initiated protocols for sickle cell vaso-occlusive pain episodes in a pediatric emergency department. *Am J Hematol*. Epub ahead of print 17 May 2018. DOI: 10.1002/ajh.25144.
7. Savage WJ, Buchanan GR, Yawn BP, et al. Evidence gaps in the management of sickle cell disease: a summary of needed research. *Am J Hematol* 2015; 90(4): 273–275.
8. Ballas SK, Gupta K and Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood* 2012; 120: 3647–3656.
9. Kopecky EA, Jacobson S, Joshi P, et al. Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clin Pharmacol Ther* 2004; 75(3): 140–146.
10. Somogyi AA, Barratt DT and Coller JK. Pharmacogenetics of opioids. *Clin Pharmacol Ther* 2007; 81: 429–444.
11. Han J, Zhou J, Saraf SL, et al. Characterization of opioid use in sickle cell disease. *Pharmacoepidemiol Drug Saf* 2018; 27: 479–486.
12. Allain F, Minogianis EA, Roberts DC, et al. How fast and how often: the pharmacokinetics of drug use are decisive in addiction. *Neurosci Biobehav Rev* 2015; 56: 166–179.
13. Jacobson SJ, Kopecky EA, Joshi P, et al. Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet* 1997; 350: 1358–1361.
14. Telfer P, Barroso F, Newell K, et al. Evaluation of a non-parenteral opioid analgesia protocol for acute sickle cell pain episodes in children. *J Clin Med* 2019; 8: 1728.
15. Telfer P, Bahal N, Lo A, et al. Management of the acute painful crisis in sickle cell disease – a re-evaluation of the use of opioids in adult patients. *Br J Haematol* 2014; 166(2): 157–164.
16. Lennernas B, Hedner T, Holmberg M, et al. Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol* 2005; 59(2): 249–253.
17. Kelly GS, Stewart RW, Strouse JJ, et al. Intranasal fentanyl improves time to analgesic delivery in sickle cell pain crises. *Am J Emerg Med* 2018; 36(7): 1305–1307.
18. Fein DM, Avner JR, Scharbach K, et al. Intranasal fentanyl for initial treatment of vaso-occlusive crisis in sickle cell disease. *Pediatr Blood Cancer* 2017; 64(6): 26332.
19. Telfer P, Criddle J, Sandell J, et al. Intranasal diamorphine for acute sickle cell pain. *Arch Dis Child* 2009; 94(12): 979–980.
20. Elander J, Bij D, Kapadi R, et al. Development and validation of the satisfaction with treatment for pain questionnaire (STPQ) among patients with sickle cell disease. *Br J Haematol* 2019; 187(1): 105–116.
21. Elander J, Lusher J, Bevan D, et al. Understanding the causes of problematic pain management in sickle cell disease: evidence that pseudoaddiction plays a more important role than genuine analgesic dependence. *J Pain Symptom Manage* 2004; 27(2): 156–169.
22. Gezmu M and Flournoy N. Group up-and-down designs for dose-finding. *J Stat Plan Infer* 2006; 136: 1749–1764.
23. Buchanan ID, Woodward M and Reed GW. Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. *Pediatr Blood Cancer* 2005; 45: 716–724.
24. Orringer EP, Casella JF, Ataga KI, et al. Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA* 2001; 286: 2099–2106.
25. Bartolucci P, Habibi A, Khellaf M, et al. Score predicting acute chest syndrome during vaso-occlusive crises in adult sickle-cell disease patients. *Ebiomedicine* 2016; 10: 305–311.
26. Telen MJ, Wun T, McCavit TL, et al. Randomized phase 2 study of GMI-1070 in SCD: reduction in time to resolution of vaso-occlusive events and decreased opioid use. *Blood* 2015; 125: 2656–2664.
27. Tanabe P, Silva S, Bosworth HB, et al. A randomized controlled trial comparing two vaso-occlusive episode (VOE) protocols in sickle cell disease (SCD). *Am J Hematol* 2018; 93(2): 159–168.
28. Hardwick WE Jr, Givens TG, Monroe KW, et al. Effect of ketorolac in pediatric sickle cell vaso-occlusive pain crisis. *Pediatric Emergency Care* 1999; 15: 179–182.
29. Wright SW, Norris RL and Mitchell TR. Ketorolac for sickle cell vaso-occlusive crisis pain in the emergency department: lack of a narcotic-sparing effect. *Ann Emerg Med* 1992; 21(8): 925–928.
30. Dampier CD, Smith WR, Wager CG, et al. IMPROVE trial: a randomized controlled trial of patient-controlled analgesia for sickle cell painful episodes: rationale, design challenges, initial experience, and recommendations for future studies. *Clin Trials* 2013; 10(2): 319–331.
31. Glassberg J, Simon J, Patel N, et al. Derivation and preliminary validation of a risk score to predict 30-day ED revisits for sickle cell pain. *Am J Emerg Med* 2015; 33(10): 1396–1401.
32. Smith WR, McClish DK, Dahman BA, et al. Daily home opioid use in adults with sickle cell disease: the PiSCES project. *J Opioid Manag* 2015; 11(3): 243–253.

bjh research paper

Development and validation of the Satisfaction with Treatment for Pain Questionnaire (STPQ) among patients with sickle cell disease

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Summary

A brief measure of patient satisfaction with treatment for pain is needed to help improve the treatment of painful episodes caused by sickle cell disease (SCD), especially during and after the transition from paediatric to adult care. Focus groups of 28 adolescent and adult patients were consulted about the content, clarity and relevance of 30 potential items, resulting in an 18-item version. This was validated by analysing questionnaire responses from 120 patients aged 12–53 years. Confirmatory factor analysis and item analysis indicated five subscales with high internal reliability: 'Communication and Involvement' (6 items, $\alpha = 0{\cdot}87$); 'Respect and Dignity' (3 items, $\alpha = 0{\cdot}82$); 'Pain Control' (3 items, $\alpha = 0{\cdot}91$); 'Staff Attitudes and Behaviour' (4 items, $\alpha = 0{\cdot}88$); and 'Overall Satisfaction' (2 items, $\alpha = 0{\cdot}85$) plus a Total Satisfaction score (18 items, $\alpha = 0{\cdot}96$). High negative correlations with the Picker Patient Experience Questionnaire, a measure of problem experiences, indicated good convergent validity. Lower satisfaction scores among patients aged over 18 years, those admitted via the emergency department, those treated by non-specialist hospital staff, and those reporting more breakthrough pain indicated good concurrent validity. The questionnaire provides a convenient brief measure that can be used to inform and evaluate improvements in healthcare for adolescent and adult patients with SCD, and could potentially be adapted for other painful conditions.

Keywords: sickle, pain, treatment, patient, satisfaction.

Introduction

Admission to hospital with acute pain is a frequent experience for patients with sickle cell disease (SCD), yet patients' experiences of how acute painful episodes are managed in hospital are often negative. Questionnaire, interview and focus group studies are consistent in highlighting deficiencies in knowledge, expertise and training amongst medical and nursing staff, who are also sometimes perceived by patients as unsympathetic and unwilling to believe that patients are in pain (Haywood *et al.*, 2014a; Lattimer *et al.*, 2010; Elander *et al.*, 2011).

Problematic hospital pain management for patients with SCD is an international problem that reflects a range of factors, including how hospital staff perceive and make judgements about SCD patients' pain (Elander *et al.*, 2006, 2011). Recognition of these problems has led to interventions to improve the quality of hospital care for sickling episodes, including initiatives focusing on community services (Lottenberg *et al.*, 2014), hospital emergency departments (Morris *et al.*, 2012; Tanabe *et al.*, 2012), analgesic medication management (Mager *et al.*, 2017), and staff attitudes (Haywood *et al.*, 2015; Singh *et al.*, 2016).

One study showed that satisfaction was higher among SCD patients receiving care at specialist rather than non-specialist treatment centres (Aisiku *et al.*, 2007), so it seems likely that satisfaction directly reflects quality of care. Another showed that satisfaction was associated with better treatment adherence among patients with SCD (Haywood *et al.*, 2014b), so there are multiple reasons for focusing on improving patient satisfaction in order to improve health outcomes for patients with SCD.

An important group of SCD patients who often experience poorer quality care are young people transitioning from

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paediatric to adult services (Wojciechowski *et al.*, 2002). One analysis showed that young adults had more SCD complications than paediatric patients (Blinder *et al.*, 2013), and another showed that acute care encounters, re-hospitalisations and emergency department attendance all increased around the time of transition (Brousseau *et al.*, 2010). Large cohort studies show increases in deaths among young adult SCD patients soon after the transition to adult care (Quinn *et al.*, 2010). One review of 90 young adult SCD patients showed that 20% died and 32% developed chronic pain problems within 10 years of transition (Ballas & Dampier, 2004).

Understanding the causes of poor-quality care and improving standards of care require valid and reliable measures of patients' experiences, and a Cochrane Review of pain management for SCD in children and adults recommended developing measures of pain management outcomes that are most relevant to patients and families (Dunlop & Bennett, 2006). There is also a broader trend towards greater use of patient-reported outcomes (PROs), which are any reports of patients' health status that come directly from the patient, like the Patient-Reported Outcomes Measurement Information System (PROMIS; Cella *et al.*, 2010) or the Pediatric Quality of Life Inventory (PedsQL; Varni *et al.*, 2003). PRO measures generally assess patients' symptoms, functioning or quality of life, and are often intended to inform clinical practice and individual case management as well as to evaluate services and treatment protocols (Dobrozsi & Panepinto, 2015; Elander & Spitz, 2017). Measures of patient-reported satisfaction with hospital care can therefore contribute to a developing bank of PRO measures for use to improve clinical practice and quality of care.

Some studies of SCD patients' satisfaction with care (Aisiku *et al.*, 2007; Lattimer *et al.*, 2010) have used satisfaction measures developed for general use with patients (Jenkinson *et al.*, 2002; Marshall & Hays, 1994). A satisfaction survey conducted by the UK Sickle Cell Society was designed specifically for SCD patients (Chalkley *et al.*, 2012) but not for psychometric analysis, which assesses an instrument from a measurement point of view and estimates 'reliability' (the extent to which it produces similar results under consistent conditions) and 'validity' (the extent to which it measures what it purports to measure) (Furr, 2018).

An SCD-specific measure of patient-reported quality of care that was developed from psychometric analysis of 13 items from a larger quality of life survey identified three composites: Access, Provider Interaction and Emergency Department Care (Evensen *et al.*, 2016). However, this measure asked about pain management only in the emergency department, and was developed and validated only with adult patients, whereas we wished to develop a measure of satisfaction with treatment for pain in any hospital department, which could also be used by both adolescent and adult patients to help improve SCD patients' transitions from paediatric to adult services. The aim of the present study was therefore to produce a valid and reliable measure of satisfaction with treatment for pain that was designed specifically to evaluate hospital treatment of painful sickling episodes among adolescent and adult SCD patients.

Methods

Development of the questionnaire

We adopted a deductive approach to generating content, rather than beginning with patient interviews or focus groups about experiences of care, because there is already considerable qualitative research on SCD patients' experiences of care (e.g., Maxwell *et al.*, 1999; Strickland *et al.*, 2001). A set of pre-identified potential items was therefore used to prompt and facilitate more focused consultation and discussion with patients in focus groups, which were also invited to address issues of content, for example by identifying aspects of treatment that needed to be included in addition to those already identified. The initial 'top down' approach was therefore intended to make use of existing knowledge and enable patients to contribute more effectively to the development process.

Following established good practice for scale development (DeVellis, 2012), we first identified potential questionnaire items from previous measures. These included the Picker Patient Experience Questionnaire (Jenkinson *et al.*, 2002), the Patient Satisfaction Questionnaire (Marshall & Hays, 1994) and the UK Sickle Cell Society's survey of service users (Chalkley *et al.*, 2012). This produced an initial pool of 64 potential items covering communication and involvement in care, respect and dignity, pain control, staff attitudes and behaviour, and overall satisfaction. Items that were not relevant to SCD pain were eliminated in a panel assessment process. First, each of six members of a panel rated each item as relevant or not relevant. Items the panel agreed were not relevant were eliminated, and then items the panel disagreed about were discussed to reach consensus. The criteria were that retained items should be about issues that could affect hospital treatment of painful episodes, so items specifically referring to screening, treatment of other symptoms, financial costs of care etc. were eliminated. This resulted in a shorter list of 30 potential items, with 13 about communication and involvement, 4 about respect and dignity, 3 about pain control, 3 about staff attitudes and behaviour, and 7 about overall satisfaction.

Health professionals with specific expertise in the management of SCD pain were then consulted to assess the 30 items for coverage and content validity, and to adapt wording where necessary. This was achieved by providing the 30 items with instructions about what issues to consider, and asking the subject matter experts to rate each item for relevance and make comments, in the format of the example given in Data S1.

Focus groups

Focus groups of adolescent and adult SCD patients were then consulted about the 30 items to: (i) assess item relevance, importance, comprehensibility, acceptability and usability; (ii) identify other potential aspects of treatment that should also be covered; and (iii) select a smaller number of items for a briefer measure.

This was achieved by giving each focus group participant the 30 items to look at before the meetings; they were asked to bring their copies, together with any notes, to the focus groups for discussion. The group discussions began by considering the points raised by the participants from their advance reading and went on to further discussion of the items and the issues to be considered when measuring people's satisfaction with their care in hospital during treatment for painful sickling episodes, including exploration of participants' views about their own care experiences and factors that influenced their own satisfaction with hospital care, as well as issues like wording, language and response formats.

The criteria were defined with prompts, for example: 'Is this question about something that affects how you feel about how you are looked after in hospital during a painful sickling episode?' (Relevance); 'Does this question refer to something that really makes a difference to how you feel about the hospital care?' (Importance); 'Is this question easy for you or other people to understand?' (Comprehensibility); 'Is this question saying what it means in the right way, and not being rude or strange at all?' (Acceptability); and 'Is it possible to give a proper answer to this question?' (Usability).

Focus group participants were identified from lists of patients attending sickle cell clinics at Bart's Health NHS Trust who had at least one acute painful sickling episode treated in hospital in the past two years. All potential participants or their parents/carers were given patient information sheets explaining the study and signed an informed consent form. Adolescent patients aged under 16 years signed an assent form. Separate focus groups were conducted for adolescents (aged 14–19 years) and adults (aged 20+ years). The focus group participants comprised 10 adolescents and 18 adults with SCD. Most were of African family origin and all spoke English. One adult and one adolescent focus group were held at the Royal London Hospital and the other two were held at Newham University Hospital. The focus groups lasted between 45 and 90 min, and were facilitated by two of the authors. A postgraduate student also helped to facilitate two of the groups. Participants were paid £25 each for participating, in recognition of the time and effort involved.

The discussions were audio-recorded and transcribed verbatim. Transcripts were analysed using an adaptation of the Delphi method to elicit and summarise expert opinion (Brady, 2015). This involved first identifying content in the transcripts that met the criteria for addressing relevance, importance, comprehensibility, acceptability or usability, then establishing whether or not there was reasonable consensus among participants. A descriptive thematic analysis was then applied to organise participants' contributions into themes (Braun & Clarke, 2006), which were then used as a framework for translating focus group suggestions into proposed modifications to the questionnaire.

Validation of the questionnaire

The aim of the validation phase was to test the modified questionnaire for factor structure, internal reliability, convergent validity and concurrent validity. For factor structure, we tested 1-factor, 2-factor and 5-factor models. The 1-factor model included all the items together, assuming that satisfaction is a general, uni-dimensional phenomenon. The 2-factor model comprised pain control and medication issues as one factor and interpersonal issues as another, based on a broad distinction between pharmacological pain management and more interpersonal aspects of care. The 5-factor model comprised communication and involvement, respect and dignity, pain control, staff attitudes and behaviour, and overall satisfaction, based on specific areas of content identified during the development phase.

The participants were SCD patients recruited at East London and Essex Clinical Haemoglobinopathy Network hospitals, who completed paper-based questionnaires in hospital clinics, and patients at other hospitals who were recruited via the Sickle Cell Society and completed the questionnaire online. Eligibility criteria were age 12–55 years, diagnosis of SCD (any genotype), and at least one acute painful sickling episode treated in hospital in the past two years. For those recruited via the Sickle Cell Society, an invitation message was e-mailed to eligible members and affiliates by the Society and posted on the Society web pages.

Participants were asked to report their age, gender, SCD type, family origins and place of residence. They were then asked to give information about painful episodes they had experienced in the past year and their last hospital treatment for a painful episode. Then they completed the Satisfaction with Treatment for Pain Questionnaire (STPQ) and the Picker Patient Experience Questionnaire (PPE-15; Jenkinson *et al.*, 2002). The PPE-15 is a 15-item measure of patients' experiences covering eight aspects of healthcare: information and education, coordination of care, physical comfort, emotional support, respect for patient preferences, involvement of family and friends, continuity and transition, and overall impression. Two of the response options for each question indicate a problem, one more severe than the other. Two scores can be computed to show the numbers of items for which problems were reported, each with a potential range of 0–15; one counting only more severe problems, the other counting both more and less severe problems.

Data were analysed for normality using the Kaiser-Meyer-Olkin (KMO) measure (Kaiser, 1970) and the Test of Sphericity (Bartlett, 1950). Because we wished to compare specific pre-identified factor structures, confirmatory factor

analysis was used to compare the fit between data and factor structures of the 1-, 2- and 5-factor models (Harlow, 2014).

Seven indicators of model fit were computed for each model: Chi Square (recommended value ≤3·00; Gefen *et al.*, 2000) was used to assess whether data differed from the models. The Goodness-of-Fit Index (GFI) (recommended value ≥0·90; Hoyle, 1995), Root Mean-Square Error of Approximation (RMSEA) (recommended value ≤0·06; Hu & Bentler, 1999) and Standardised Root Mean Square Residual (SRMR) (recommended value ≤0·08; Hu & Bentler, 1999) were used to assess how much of the variance in the data was explained by the models. The Comparative Fit Index (CFI) (recommended value ≥0·95; Hu & Bentler, 1999), Tucker Lewis Index (TLI) (recommended value ≥0·95; Hu & Bentler, 1999) and Normed Fit Index (NFI) (recommended value ≥0·95; Hu & Bentler, 1999) were used to test the models against the worst possible model outcome. The Maximum Likelihood estimator method was used in each case (Brown, 2015). For data scaling, the first variable for each scale was set at one.

The internal reliability or internal consistency of each factor (the extent to which a given group of items measure the same thing) was assessed by computing Cronbach's Alpha. For the model with the best fit to the data, subscale scores were computed by summing across the items in each factor, with higher scores indicating greater satisfaction. Convergent validity was assessed by examining relationships between STPQ scores and PPE-15 scores using Pearson correlations. We predicted negative correlations because STPQ scores measure satisfaction and PPE-15 scores measure problematic experiences. Concurrent validity was assessed by comparing STPQ scores between patients with different specific experiences and histories of treatment, using *t* tests and Pearson correlations. This bi-variate approach, testing associations between satisfaction and individual variables, was chosen to give the most comprehensive picture of concurrent validity, in which all the patient and treatment factors associated with STPQ scores would be identified, and also to test a number of specific predictions. Based on previous evidence about factors affecting quality of pain management for SCD, we predicted that STPQ scores would be:

1 Higher among younger participants treated in paediatric hospital wards (Wojciechowski *et al.*, 2002; Blinder *et al.*, 2013);
2 Lower among participants admitted to hospital via Accident and Emergency departments (Aisiku *et al.*, 2009; Glassberg *et al.*, 2013);
3 Lower among participants treated with shorter-acting analgesics and delivery methods (Rees *et al.*, 2003; Sickle Cell Society, 2008);
4 Lower among participants reporting adverse effects of hospital pain management (Krishnamurti *et al.*, 2014; Whelan *et al.*, 2004).

Ethics and governance

The study protocol was approved by the National Health Service (NHS) National Research Ethics Committee (Ref 14/YH/1288) and by the NHS Health Research Authority, and was sponsored by Bart's Health NHS Trust. The main source of funding was a strategic research grant from Bart's Charity. Funders had no part in drafting or reviewing the protocol, conducting the study or analysing and reporting results.

Results

Focus groups

The themes that resulted from the analysis of focus group data were: (i) *content* – questions that should be retained or discarded, and topic areas that needed to be covered; (ii) *modification of existing questions*; and (iii) *technical aspects*, including clarity (making the meaning of questions quickly and easily grasped), repetition (ensuring that each question addressed a distinct issue), overall length (making each question as brief and concise as possible), and interpretation (avoiding ambiguous wording and statements that could have different meanings). These provided a framework for organising specific proposed modifications, which were checked to ensure they captured the intentions of a consensus of participants before being implemented. A commentary on focus group feedback is given in Data S2.

The resulting 18 items are given below, for use with 5-point response scales: 'strongly agree' (coded 5), 'agree' (4), 'not sure' (3), 'disagree' (2), 'strongly disagree' (1). The instructions were 'Please think about the last time you were in hospital for a painful episode, and tick one box for each statement to show how much you agree or disagree'.

1 I was satisfied with the communication between me and the people looking after me.
2 I felt comfortable enough to ask questions.
3 When I asked questions, I got answers I could understand.
4 The people looking after me spent enough time with me.
5 The people looking after me treated me with respect and dignity.
6 The people looking after me had a good attitude.
7 I was involved enough in decisions about my treatment and care.
8 I was told enough about my medications.
9 The people looking after me responded to my pain in good time.
10 The people looking after me believed how serious my pain was.
11 The people looking after me did everything they could to control my pain.
12 Overall I was satisfied with how my pain was treated.
13 The people looking after me knew enough about my condition.

14 I felt good about the knowledge and ability of the people looking after me.
15 The people looking after me were careful to check everything when treating me.
16 I or my family had all the information we needed when I left hospital.
17 Overall, I was happy with the support and care I received.
18 I would recommend the hospital to other people with sickle cell disease.

The 18-item STPQ was completed by 120 SCD patients: 94 (78%) completed paper-based versions in hospital clinics and 26 (22%) completed the questionnaire online. Characteristics of the participants completing paper-based and online versions of the questionnaire, and tests of differences between them, are shown in Table I.

Compared with participants who completed paper-based versions, respondents to the online survey were more likely to be female and were older, with fewer individuals aged under 18 years, and less likely to have African family origins. They were also less likely to live in London, to attend hospital in London, and to have arrived at hospital via the accident and emergency department at their last admission. However the groups did not differ significantly in the proportions who were married or cohabiting or who had HbSS genotype, nor how many painful episodes they had in the last year or how many nights they spent in hospital during their last admission.

Factor structure

The Kaiser-Meyer-Olkin (KMO) value was 0·944, showing adequate sampling (Field, 2013; Hutcheson & Sofroniou, 1999). Bartlett's test of Sphericity was highly significant ($\chi^2 = 1810{\cdot}28$, $df = 153$, $P < 0{\cdot}001$) indicating that the correlations were significantly different from zero, making factor analysis appropriate. Table II shows values of seven fit indices along with the values they should be at least 'close to' for a good fit between model and data (Hu & Bentler, 1999). The 1-factor model comprised all 18 items. The 2-factor model comprised Pain Control and Medication (Questions 8, 9, 10, 11 and 12) and Interpersonal Issues (Questions 1, 2, 3, 4, 5, 6, 7, 13, 14, 15, 16, 17 and 18). The 5-factor model comprised Communication and Involvement (Questions 1, 2, 3, 7, 8 and 16), Respect and Dignity (Questions 4, 5 and 6), Pain Control (Questions 9, 11 & 12), Staff Attitudes and Behaviour (Questions 10, 13, 14 and 15) and Overall Satisfaction (Questions 17 and 18).

While χ^2 was significant in each case, indicating differences between the data and the model, χ^2 was much lower for the 5-factor model than both the 1-factor and 2-factor models, showing that the 5-factor model was a better fit to the data. Indeed, for all the other fit indices, the values for the 5-factor model were more favourable than those for the 1-factor or 2-factor models, suggesting that the 5-factor model fitted the data better than the other models. For one of the indices (SRMR), the value for the 5-factor model exceeded the recommended value, and for the remainder they were close to recommended values, indicating the 5-factor model was an acceptable, though not ideal, fit to the data.

Cronbach's alpha coefficients, measuring internal consistency or internal 'reliability', for the five factors were: Communication and Involvement 0·87; Respect and Dignity 0·82, Pain Control 0·91, Staff Attitudes and Behaviour 0·88, Overall Satisfaction 0·85. Cronbach's alpha for the two factors were 0·92 for Pain Control and Medication and 0·94 for

Table I. Demographic and other features of participants in the validation phase.

	Paper-based	Online	χ^2 or t	Total
Patients, *n* (%)	94 (78·3%)	26 (21·7%)	–	120
Female, *n* (%)	51 (54·3%)	21 (80·8%)	$\chi^2 = 5{\cdot}97$*	72 (60·0%)
Age, years; mean (SD)	22·72 (8·76)	30·50 (11·83)	$t = 3{\cdot}12$**	24·4 (9·98)
Age <18 years, *n* (%)	38 (40·4%)	4 (15·4%)	χ^2=5·61*	42 (35·0%)
Age <16 years, *n* (%)	16 (17·0%)	3 (11·5%)	$\chi^2 = 0{\cdot}14$	19 (15·8%)
Married/co-habiting, *n* (%)	8 (8·5%)	6 (23·1%)	$\chi^2 = 2{\cdot}90$	14 (11·7%)
Living in London, *n* (%)	88 (93·6%)	12 (46·2%)	$\chi^2 = 29{\cdot}71$***	100 (83·3%)
African family origin, *n* (%)	81 (86·2%)	16 (61·5%)	$\chi^2 = 6{\cdot}47$***	97 (80·8%)
HbSS genotype, *n* (%)†	81 (89·0%)	19 (73·1%)	$\chi^2 = 2{\cdot}95$	100 (85·5%)
Attending London hospital, *n* (%)	93 (98·9%)	12 (46·2%)	$\chi^2 = 47{\cdot}16$***	105 (87·5%)
Arrived in hospital via A and E, *n* (%)†	80 (87·9%)	17 (65·4%)	$\chi^2 = 5{\cdot}74$*	97 (82·9%)
Painful episodes last year when did not see doctor, mean (SD)	6·70 (8·57)	6·96 (10·38)	$t = 0{\cdot}13$	6·76 (8·95)
Painful episodes last year when did see doctor, mean (SD)	4·21 (6·56)	3·39 (3·61)	$t = 0{\cdot}61$	4·02 (6·01)
N nights in hospital last admission, mean (SD)	5·55 (5·38)	4·92 (7·12)	$t = 0{\cdot}48$	5·40 (5·60)

†$N = 117$ because three participants did not give information about their SCD genotype or how they arrived in hospital.
*$P < 0{\cdot}05$.
**$P < 0{\cdot}01$.
***$P < 0{\cdot}001$.

Table II. Fit indices and recommended values.

Fit indices	1-factor	2-factor	5-factor	Recommended values	Source
χ^2	319·64	307·757	251·974	≤3·00	Gefen *et al* (2000)
df	135	134	125	N/A	N/A
P	<0·001	<0·001	<0·001	>0·05	N/A
GFI	0·774	0·783	0·820	≥0·90	Hoyle (1995)
RMSEA	0·107	0·104	0·092	≤0·06	Hu and Bentler (1999)
SRMR	0·052	0·053	0·049	≤0·08	Hu and Bentler (1999)
CFI	0·896	0·903	0·929	≥0·95	Hu and Bentler (1999)
TLI	0·883	0·889	0·913	≥0·95	Hu and Bentler (1999
NFI	0·835	0·841	0·870	≥0·95	Hu and Bentler (1999)

χ^2, Chi Squared; *df*, degrees of freedom; *P*, probability; GFI, Goodness of fit index; RMSEA, root mean squared error of approximation; SRMR, standardized root mean squared residual; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; NFI, Normed Fit Index.

Interpersonal Factors. Cronbach's alpha for the 18-item total was 0·96. These show that five subscales and the total score had very high internal consistency. Descriptive statistics for the five subscales and total score (computed by summing across items) are given in Table III. Higher scores indicate greater satisfaction in each case.

Convergent validity

The first score derived from the PPE-15 questionnaire, which counted only responses indicating more severe problems, ranged from 0 to 13 with a mean of 2·76 (standard deviation [SD] 2·66). The second, which counted responses indicating both more and less severe problems, ranged from 0 to 15 with a mean of 8·08 (SD 4·25). The correlations between STPQ scores and the first PPE-15 score ranged from −0·610 for Staff Attitudes and Behaviour to −0·691 for Total Satisfaction, and those between STPQ scores and the second PPE-15 score ranged from −0·544 for Overall Satisfaction to −0·677 for Total Satisfaction, with $P < 0·001$ in each case. For both PPE-5 scores, the highest correlation was with Total Satisfaction. The correlations between STPQ scores and PPE-15 scores were similar in size to the correlation between the two PPE-15 scores, which was 0·626.

Concurrent validity

Because there were six questionnaire scores for each person (five subscales and a Total Satisfaction score), we adjusted the critical value of *P* to 0·0083 (0·05 divided by 6) for all the tests in which STPQ scores were compared between groups of participants or correlated with other measures (Bonferroni, 1936).

We first examined possible differences in satisfaction scores between demographic sub-groups. Mean STPQ scores for male and female participants, and those aged under and over 18 years are shown in Tables IV and V. Male participants had higher scores than females for Communication and Involvement. Participants aged under 18 years had higher scores for Respect and Dignity, Pain Control, Staff Attitudes and Behaviour, and Total Satisfaction, but not Communication and Involvement or Overall Satisfaction. Age in years was also negatively correlated with Respect and Dignity ($r = −0·28$, $P = 0·002$), Staff Attitudes and Behaviour ($r = −0·24$, $P = 0·007$) and Total Satisfaction (−0·24, $P = 0·007$).

Table III. Subscale and total satisfaction scores.

	Minimum–Maximum	Mean (SD)
Communication and involvement	7–30	23·39 (4·54)
Respect and dignity	3–15	10·99 (2·87)
Pain control	3–15	10·69 (3·22)
Staff attitudes and behaviour	4–20	14·77 (3·83)
Overall satisfaction	2–10	7·73 (2·09)
Total satisfaction	21–90	67·57 (15·13)

SD, standard deviation.

Participants who were single had higher scores than those who were married or cohabiting for Respect and Dignity, Overall Satisfaction and Total Satisfaction (group means and significance tests are given in Data S3). However, there were only 14 participants who were married or cohabiting, and those who were single were also significantly younger than those who were married or cohabiting (mean 22·71 years [SD 8·70] compared with 37·29 [SD 9·96]; $t = 5·80$, $P < 0·001$), so the differences between groups may have reflected age differences as much as relationship status differences.

There were no significant differences in STPQ subscale or total scores between those who completed the questionnaire online versus in hospital clinics, nor between those with African versus other family origins, or those living in London versus outside London, or those attending hospitals in London versus outside London (group means and significance tests are given in Data S3).

We next examined relationships between STPQ scores and participants' histories of painful episodes and treatment

during their last hospital admission. Participants who arrived in hospital via the Accident and Emergency department had lower scores for Respect and Dignity, Pain Control, Staff Attitudes and Behaviour, Overall Satisfaction and Total Satisfaction (Table VI). Participants treated by general doctors and nurses had lower satisfaction scores for Communication and Involvement, Respect and Dignity, Staff Attitudes and Behaviour, and Total Satisfaction (Table VII).

Frequency of breakthrough pain was correlated with Communication and Involvement ($r = -0{\cdot}259$, $P = 0{\cdot}005$), Respect and Dignity ($r = -0{\cdot}317$, $P < 0{\cdot}001$), Pain ($r = -0{\cdot}414$, $P < 0{\cdot}001$), Staff ($r = -0{\cdot}292$, $P = 0{\cdot}001$), Overall Satisfaction ($r = -0{\cdot}244$, $P = 0{\cdot}008$) and Total Satisfaction ($r = -0{\cdot}333$, $P < 0{\cdot}001$), but STPQ scores were not correlated with how often participants experienced side effects of analgesics.

There were also no significant correlations between STPQ scores and numbers of painful episodes in the last year where participants saw a doctor or went to hospital, nor those where participants did not see a doctor or go to hospital. Scores were also not correlated with the number of nights participants spent in hospital in their last admission, and they did not differ significantly between participants who were and were not treated in each of Accident and Emergency, a general ward, or a specialist haematology ward (correlations, group means and significance tests are given in Data S4).

STPQ scores also did not differ between participants who were and were not treated with morphine, diamorphine, oxycodone, pethidine or fentanyl. Participants treated with subcutaneous analgesics had lower satisfaction scores for Respect and Dignity, but scores did not differ between participants who were and were not treated with oral, intramuscular, intranasal or sublingual analgesics, or with continuously infused or patient-controlled analgesics (group means and significance tests are given in Data S5).

Table IV. Mean (standard deviation) scores for male ($n = 48$; 40%) and female ($n = 72$; 60%) participants.

	Male	Female	*t*
Communication and involvement	24·75 (3·61)	22·49 (4·88)	2·75*
Respect and dignity	11·81 (2·50)	10·44 (2·99)	2·62
Pain control	11·06 (2·97)	10·44 (3·37)	1·03
Staff attitudes and behaviour	15·81 (3·25)	14·07 (4·05)	2·49
Overall satisfaction	8·17 (1·80)	7·44 (2·23)	1·88
Total satisfaction	71·60 (12·39)	64·89 (16·24)	2·43

*$P < 0{\cdot}0083$ (0·05 divided by 6).

Table V. Mean (standard deviation) scores for participants aged under ($n = 42$; 35%) and over ($n = 78$; 65%) 18 years.

	<18 years	≥18 years	*t*
Communication and involvement	24·60 (4·14)	22·74 (4·64)	2·17
Respect and dignity	12·24 (2·50)	10·32 (2·85)	3·66*
Pain control	11·91 (2·77)	10·04 (3·27)	3·30*
Staff attitudes and behaviour	16·48 (3·59)	13·85 (3·66)	3·78*
Overall satisfaction	8·36 (1·83)	7·40 (2·15)	2·45
Total satisfaction	73·57 (13·83)	64·35 (14·89)	3·32*

*$P < 0{\cdot}0083$ (0·05 divided by 6).

Table VI. Mean (standard deviation) scores for participants who did ($n = 97$; 82·9%) and did not ($n = 20$; 17·1%) arrive in hospital via the Accident and Emergency (A and E) department.†

	Arrived via A and E	Did not arrive via A and E	*t*
Communication and involvement	22·92 (4·66)	25·15 (3·48)	2·03
Respect and dignity	10·57 (2·95)	12·65 (1·63)	4·41*
Pain control	10·20 (3·28)	12·60 (1·90)	4·45*
Staff attitudes and behaviour	14·20 (3·88)	17·05 (2·61)	4·06*
Overall satisfaction	7·45 (2·18)	8·85 (1·04)	4·35*
Total satisfaction	65·33 (15·49)	76·30 (8·85)	4·34*

†$N = 117$ because three participants did not give information about how they arrived in the hospital.
*$P < 0{\cdot}0083$ (0·05 divided by 6).

Table VII. Mean (standard deviation) scores for participants treated (n = 83; 70·3%) and not treated (n = 35; 29·7%) by general (not specialist) doctors and nurses.†

	Treated by general doctors and nurses	Not treated by general doctors and nurses	t
Communication and involvement	22·41 (4·73)	25·57 (3·21)	3·62*
Respect and dignity	10·46 (2·88)	12·14 (2·57)	2·99*
Pain control	10·19 (3·12)	11·71 (3·26)	2·39
Staff attitudes and behaviour	13·95 (3·89)	16·57 (3·12)	3·53*
Overall satisfaction	7·45 (2·07)	8·34 (2·06)	2·15
Total satisfaction	64·46 (15·14)	74·34 (13·15)	3·37*

†N = 118 because two participants did not give information about being treated by general doctors and nurses.
*P < 0·0083 (0·05 divided by 6).

Table VIII. Summary of associations between STPQ scores and other measures.

	STPQ subscales					
	Communication and involvement	Respect and dignity	Pain control	Staff attitudes and behaviour	Overall satisfaction	Total satisfaction score
Female	Less satisfied					
Aged over 18 years		Less satisfied	Less satisfied	Less satisfied		Less satisfied
Married or cohabiting		Less satisfied			Less satisfied	Less satisfied
Admitted via A and E		Less satisfied	Less satisfied	Less satisfied	Less satisfied	Less satisfied
Treated by general staff	Less satisfied	Less satisfied		Less satisfied		Less satisfied
Subcutaneous analgesics		Less satisfied				
Breakthrough pain	Less satisfied	Less satisfied	Less satisfied	Less satisfied	Less satisfied	Less satisfied

The pattern of associations between STPQ scores and other measures is summarised in Table VIII. This shows that Respect and Dignity was the STPQ subscale most sensitive to influence, followed by Total Satisfaction, then Staff Attitudes and Behaviour. More frequent breakthrough pain influenced all six of the satisfaction measures, and arriving in hospital via Accident and Emergency influenced five out of six. Being older than 18 years was associated with lower satisfaction for Respect and Dignity, Pain Control, and Staff Attitudes and Behaviour. Being female was associated only with lower satisfaction for Communication and Involvement, and being treated with subcutaneous analgesics was associated only with lower satisfaction for Respect and Dignity.

Discussion

The factor analysis and item analysis supported a 5-factor structure, making the scale a simple, brief measure of several key aspects of patient satisfaction, each with very good internal reliability. Convergent validity was supported by highly significant negative correlations with scores from the PPE-15, which is a widely used and positively evaluated measure of patient experiences in healthcare (Beattie *et al.*, 2015).

Concurrent validity was supported by predicted relationships with participants' recent hospital experiences: four of the six satisfaction scores were higher among participants under 18 years old, supporting prediction one; five scores were lower among patients admitted via the accident and emergency department, supporting prediction two; four scores were lower among patients treated by general rather than specialist staff and all six scores were lower among patients who experienced more breakthrough pain, supporting prediction four. However, the only analgesic type or delivery method associated with satisfaction was subcutaneous administration of analgesics, which was associated only with lower Respect and dignity, so there was little support for prediction three.

These findings are consistent with research showing that quality of care is reduced when patients transition from paediatric to adult services (Wojciechowski *et al.*, 2002; Blinder *et al.*, 2013), and that patients have poorer experiences in hospital emergency departments (Aisiku *et al.*, 2009; Glassberg *et al.*, 2013) and when their pain is less well controlled (Krishnamurti *et al.*, 2014; Whelan *et al.*, 2004). The scale's validity as a specific measure of satisfaction with treatment for pain was also supported by the fact that scores were not related to more general measures of illness severity, such as numbers of painful episodes or nights spent in hospital.

The STPQ has a strong emphasis on behavioural and interpersonal aspects of care, as do the Patient Satisfaction Questionnaire (PSQ; Marshall & Hays, 1994), the PPE-15 (Jenkinson *et al.*, 2002), and the ASCQ-Me Quality of Care survey (Evensen *et al.*, 2016). However, the PSQ does not ask about pain at all, the PPE-15 has just one question about pain and the ASCQ-Me Quality of care survey has three items about pain but all three are about pain in the

emergency room. Two of these loaded on the Emergency Department Care composite and the third loaded on the Access composite ('what is the longest you had to wait in the emergency room before your pain was treated') (Evensen *et al.*, 2016). By comparison with those measures, the STPQ was specifically designed to measure satisfaction with treatment for pain and includes 4 items about pain and a specific 3-item subscale dealing specifically with pain control. (One item about pain is in the Staff Attitudes and Behaviour subscale; Question 10: 'The people looking after me believed how serious my pain was.') The STPQ asks about treatment of pain in hospital generally, not just the emergency department, so it could be used to compare experiences between patients treated in different hospital wards or departments, or those admitted to hospital in different ways.

The STPQ was developed in close consultation with SCD patients in order to identify aspects of care that impact on patients' hospital experiences, consistent with the recommendations of a Cochrane Review (Dunlop & Bennett, 2006). This is the reason for the inclusion of so many items that do not deal specifically with pain management, for the focus group consultation revealed the extent to which interpersonal and non-pharmacological aspects of hospital care influence patients' experiences of treatment for pain. Given that, as a measure of hospital treatment of pain, the STPQ includes so many items dealing with interpersonal and other aspects of treatment not directly and specifically related to the clinical/pharmacological management of pain, one might ask why we did not begin with an existing PRO measure. For example, global and disease-specific PRO measures, including pain and fatigue, were used to inform the improved clinical management of a teenage boy with SCD in one example (Dobrozsi & Panepinto, 2015). However, the PROs used in that example provided information about the patients' own symptoms, functioning, quality of life, etc., which could be used to direct, tailor or coordinate care, whereas a measure of satisfaction with care, such as the STPQ, provides information about patients' direct experience of care, rather than their own health and wellbeing.

The ASCQ-Me Quality of Care survey and the STPQ have a number of similarities but also deal with subtly different aspects of hospital care; the ASCQ-Me Quality of Care survey was developed from existing PRO measures and has a special focus on pain management in emergency departments, whereas the STPQ focuses on the hospital treatment of painful episodes, including during hospital admissions as well as in outpatient clinics and emergency departments. Also, the STPQ was designed to measure satisfaction with treatment for pain among adolescents and adults with SCD, so that it could be used in research and practice to improve transitions from paediatric to adult hospital services for SCD.

The approach we adopted was neither wholly bottom-up nor wholly top-down, but rather a hybrid as we began in a top-down way with items selected as relevant from existing measures, then developed from that starting point in a more bottom-up way with direct input from patients. The STPQ can contribute to a growing number of patient-reported outcome measures suitable for SCD, including the PROMIS, the PedQL and the ASCQ-Me Quality of Care survey. All these measures can contribute to improving clinical practice and quality of care, but the STPQ is best suited for evaluations of care for painful episodes across different hospital departments, including paediatric and adult services.

The study does have some limitations. First, it was a questionnaire study, so all the data were self-reported. This is arguably the only approach to measuring patient satisfaction, but certain information, e.g. SCD genotype, could be recorded more reliably from medical records or laboratory tests, for there is evidence of misreporting of SCD status among people recruited from the general population (Bean *et al.*, 2014). However, 78% (94/120) of the participants in the validation study were recruited and completed questionnaires in hospitals where they were known as patients, so the scope for misreporting SCD status is very small, although it is possible that some participants could have confused HbSS and HbSC genotypes.

Second, in the confirmatory factor analysis, the models were all approximate fits, and no model was an ideal fit. In these circumstances, exploratory factor analysis is sometimes performed after the confirmatory factor analysis to identify a best fitting model (e.g. Evensen *et al.*, 2016). We decided against this because we began with hypothesised models for which confirmatory analyses were the appropriate tests (Kline, 2014), and combining confirmatory and exploratory factor analyses of the same data is not regarded as good practice (Worthington & Whittaker, 2006).

Hu and Bentler (1999) point out that testing model fit by applying absolute cut-off values for fit indices is 'arbitrary', and it has been suggested that fit indices should be treated as guides rather than cut-offs, as model complexity and sample size can affect their values (Brown, 2015). Hu and Bentler (1999) instead recommend considering combinations of fit indices to minimise the probability of type I and type II error. They do not actually define 'close to', but the differences between our values and the recommended values are genuinely small in several cases (CFI 0·929 compared with 0·95; TLI 0·913 compared with 0·95; NFI 0·870 compared with 0·95), and our values are at the upper end of the range of values considered by Hu and Bentler (1999). The analyses also allowed us to discriminate between models because fit indices can be used to test competing models (Worthington & Whittaker, 2006).

Whereas the fit indices were less than ideal in most cases, the Cronbach's Alpha coefficients of internal reliability were extremely high. These indicate the internal consistency of items within each individual subscale, whereas the model fit indices assess the model as a whole. This indicates that each of the five subscales and the total score had very high internal consistency, even though the overall fit of the five-factor model could be better.

Third, the tests of convergent validity were correlations between the STPQ and PPE-15 scores. The PPE-15 was one of the measures employed in the development phase, so it could be argued that this is not a strong test of convergent validity. However, the two measures do not in fact have any items in common, and although they both deal with patients' experiences of hospital care, they are, in some ways, quite different. For example, the PPE-15 asks direct questions about specific negative experiences with responses options like, 'yes always', 'yes sometimes', or 'no', whereas the STPQ presents positive statements with response options on a five-point 'strongly agree' to 'strongly disagree' scale.

Fourth, the tests of concurrent validity were bivariate rather than multivariate. This identified all the individual factors associated with STPQ scores and enabled us to test specific predictions, but it does not give a broader picture of how patient and treatment factors influence satisfaction together. Future research could use multivariate models to identify such relationships or test models of how different factors act together to influence patient satisfaction with treatment.

The STPQ and scoring instructions are given in Data S6. Future research could also examine the detail of patients' experiences that are associated with high and low satisfaction scores, e.g. by conducting content analyses of responses to the open-format parts of the questionnaire to explore the reasons for high and low scores. Further research could also assess the scale with other groups of patients treated in hospital for pain, e.g. those with cancer, joint pain or other chronic pain syndromes, for the only change needed to adapt the scale for other conditions is to replace the words 'sickle cell disease' in the final question with 'my condition' or the name of another illness. However, considering that the entire development and validation process was conducted with SCD patients, a version adapted for other pain conditions would need to be validated for those conditions.

In conclusion, the STPQ provides a convenient brief measure of patients' satisfaction with hospital treatment for painful sickling episodes, which can be used in research and practice to understand better what influences patient satisfaction and to improve healthcare for patients with SCD.

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Conflict of interest

The authors stated that they had no interests that might have been perceived as posing a conflict or bias.

Author contributions

JE and PT were responsible for the study protocol. PT and BK identified potential patients and recruited patients into the study. DB, RK, AO and NK were responsible for the data collection. MBS was responsible for the confirmatory factor analysis. JE was responsible for analysing the data and writing the manuscript. PT edited the manuscript. All the authors reviewed the manuscript and approved the final version.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Illustration of the instructions and format in which potential items were presented to subject matter experts.

Data S2. Commentary on patients' feedback during focus groups.

Data S3. Satisfaction with Treatment for Pain Questionnaire (STPQ) scores in relation to demographic and other patient factors.

Data S4. STPQ scores in relation to participants' treatment histories.

Data S5. STPQ scores in relation to treatment with different analgesics and delivery methods.

Data S6. The Satisfaction with Treatment for Pain Questionnaire (STPQ).

References

Aisiku, I.P., Penberthy, L.T., Smith, W.R., Bovbjerg, V.E., McClish, D.K., Levenson, J.L., Roberts, J.D. & Roseff, S.D. (2007) Patient satisfaction in specialized versus nonspecialized adult sickle cell care centers: the PiSCES study. *Journal of the National Medical Association*, **99**, 886.

Aisiku, I.P., Smith, W.R., McClish, D.K., Levenson, J.L., Penberthy, L.T., Roseff, S.D., Bovbjerg, V.E. & Roberts, J.D. (2009) Comparisons of high versus low emergency department utilizers in sickle cell disease. *Annals of Emergency Medicine*, **53**, 587–593.

Ballas, S.K. & Dampier, C. (2004) Outcome of transitioning paediatric patients with sickle cell disease to adult programs. *Blood*, **104**, 3743.

Bartlett, M.S. (1950) Tests of significance in factor analysis. *British Journal of Statistical Psychology*, **3**, 77–85.

Bean, C.J., Hooper, W.C., Ellingsen, D., DeBaun, M.R., Sonderman, J. & Blot, W.J. (2014) Discordance between self-report and genetic confirmation of sickle cell disease status in African-American adults. *Public Health Genomics*, **17**, 169–172.

Beattie, M., Murphy, D.J., Atherton, I. & Lauder, W. (2015) Instruments to measure patient experience of healthcare quality in hospitals: a systematic review. *Systematic Reviews*, **4**, 97.

Blinder, M.A., Vekeman, F., Sasane, M., Trahey, A., Paley, C. & Duh, M.S. (2013) Age-related treatment patterns in sickle cell disease patients and the associated sickle cell complications and healthcare costs. *Paediatric Blood & Cancer*, **60**, 828–835.

Bonferroni, C. (1936) Teoria statistica delle classi e calcolo delle probabilita. *Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commericiali di Firenze*, **8**, 3–62.

Brady, S.R.. (2015). Utilizing and adapting the Delphi method for use in qualitative research. *International Journal of Qualitative Methods*, 10 Dec 2015 https://doi.org/10.1177/1609406915621381.

Braun, V. & Clarke, V. (2006) Using thematic analysis in psychology. *Qualitative Research in Psychology*, **3**, 77–101.

Brousseau, D.C., Owens, P.L., Mosso, A.L., Panepinto, J.A. & Steiner, C.A. (2010) Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*, **303**, 1288–1294.

Brown, T.A. (2015) Methodology in the Social Sciences. Confirmatory Factor Analysis for Applied Research, 2nd edn. The Guilford Press, New York, NY, USA.

Cella, D., Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., Amtmann, D., Bode, R., Buysse, D., Choi, S. & Cook, K. (2010) The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *Journal of Clinical Epidemiology*, **63**, 1179–1194.

Chalkley, S., Nkohkwo, A., Olason, C. & Phekoo, K. (2012) The Comprehensive Care Project Working Together to Help Improve the NHS: Sickle Cell Service Users - Satisfaction Survey of a Patient's Visit to NHS. East Midlands Sickle Cell and Thalassaemia Network, UK. The Sickle Cell Society, London.

DeVellis, R.F. (2012) Scale Development. Theory and Applications. Sage Publications, London.

Dobrozsi, S. & Panepinto, J. (2015) Patient-reported outcomes in clinical practice. *ASH Education Program Book*, **2015**, 501–506.

Dunlop, R.J. & Bennett, K.C. (2006) Pain management for sickle cell disease. *Acute Pain*, **8**, 134.

Elander, J. & Spitz, E. (2017) Patient-reported outcomes: clinical applications in the field of chronic pain self-management (chapter 18). In: Perceived Health and Adaptation in Chronic Disease (eds. by F.Guillemin, A.Leplege, S.Briancon, E.Spitz & J.Coste), pp. 276–293. Routledge, Taylor and Francis Group, London, UK. ISBN 978-1-498-77898-5 (Hb)-315-15507-4 (e-book).

Elander, J., Marczewska, M., Amos, R., Thomas, A. & Tangayi, S. (2006) Factors affecting hospital staff judgements about sickle cell disease pain. *Journal of Behavioral Medicine*, **29**, 203–214.

Elander, J., Beach, M.C. & Haywood, C. Jr (2011) Respect, trust, and the management of sickle cell disease pain in hospital: comparative analysis of concern-raising behaviors, preliminary model, and agenda for international collaborative research to inform practice. *Ethnicity & Health*, **16**, 405–421.

Evensen, C.T., Treadwell, M.J., Keller, S., Levine, R., Hassell, K.L., Werner, E.M. & Smith, W.R. (2016) Quality of care in sickle cell disease: cross-sectional study and development of a measure for adults reporting on ambulatory and emergency department care. *Medicine*, **95**, e4528.

Field, A. (2013) Discovering Statistics Using IBM SPSS Statistics. Sage Publications, London.

Furr, R.M. (2018) Psychometrics: An Introduction, 3rd edn. Sage Publications, Thousand Oaks, CA, USA.

Gefen, D., Straub, D. & Boudreau, M.-C. (2000) Structural equation modeling and regression: Guidelines for research practice. *Communications of the Association for Information Systems*, **4**, 7.

Glassberg, J.A., Tanabe, P., Chow, A., Harper, K., Haywood, C. Jr, DeBaun, M.R. & Richardson, L.D. (2013) Emergency provider analgesic practices and attitudes toward patients with sickle cell disease. *Annals of Emergency Medicine*, **62**, 293–302.

Harlow, L.L. (2014) The Essence of Multivariate Thinking: Basic Themes and Methods. Routledge, New York, NY, USA.

Haywood, C., Diener-West, M., Strouse, J., Carroll, C.P., Bediako, S., Lanzkron, S., Haythornthwaite, J., Onojobi, G., Beach, M.C., Woodson, T. & Wilks, J. (2014a) Perceived discrimination in health care is associated with a greater burden of pain in sickle cell disease. *Journal of Pain and Symptom Management*, **48**, 934–943.

Haywood, C., Lanzkron, S., Bediako, S., Strouse, J.J., Haythornthwaite, J., Carroll, C.P., Diener-West, M., Onojobi, G., Beach, M.C. & Investigators, I.M.P.O.R.T. (2014b) Perceived discrimination, patient trust, and adherence to medical recommendations among persons with sickle cell disease. *Journal of General Internal Medicine*, **29**, 1657–1662.

Haywood, C., Williams-Reade, J., Rushton, C., Beach, M.C. & Geller, G. (2015) Improving clinician attitudes of respect and trust for persons with sickle cell disease. *Hospital Paediatrics*, **5**, 377–384.

Hoyle, R.H. (1995) Structural Equation Modeling: Concepts, Issues, and Applications. Sage Publications, London, UK.

Hutcheson, G.D. & Sofroniou, N. (1999) The Multivariate Social Scientist: Introductory Statistics Using Generalized Linear Models. Sage, London, UK.

Hu, L. & Bentler, P.M. (1999) Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, **6**, 1–55.

Jenkinson, C., Coulter, A. & Bruster, S. (2002) The Picker Patient Experience Questionnaire: development and validation using data from in-patient surveys in five countries. *International Journal for Quality in Health Care*, **14**, 353–358.

Kaiser, H.F. (1970) A second generation little jiffy. *Psychometrika*, **35**, 401–415.

Kline, P. (2014) An Easy Guide to Factor Analysis. Routledge, London, UK.

Krishnamurti, L., Smith-Packard, B., Gupta, A., Campbell, M., Gunawardena, S. & Saladino, R. (2014) Impact of individualized pain plan on the emergency management of children with sickle cell disease. *Pediatric Blood & Cancer*, **61**, 1747–1753.

Lattimer, L., Haywood, C. Jr, Lanzkron, S., Ratanawongsa, N., Bediako, S.M. & Beach, M.C. (2010) Problematic hospital experiences among adult patients with sickle cell disease. *Journal of Health Care for the Poor and Underserved*, **21**, 1114–1123.

Lottenberg, R., Krywicki, R., Doad, G., Kabange, W., Modupe, M., Steele, G., McGriff, K.Z., Sirleaf, A.J., Kutlar, A., Gibson, R., Clair, B. & Lyon, L.M. (2014) Implementation of a community hospital-based fast track pathway for the treatment of acute pain episodes in adults with sickle cell disease. *Blood*, **124**, 4854–4854.

Mager, A., Pelot, K., Koch, K., Miller, L., Hubler, C., Ndifor, A., Coan, C., Leonard, C. & Field, J.J. (2017) Opioid management strategy decreases admissions in high-utilizing adults with sickle cell disease. *Journal of Opioid Management*, **13**, 143–156.

Marshall, G. & Hays, R.D. (1994) The Patient Satisfaction Questionnaire Short-Form (PSQ-18).

RAND, Santa Monica, CA, USA. Available at: https://www.rand.org/content/dam/rand/pubs/papers/2006/P7865.pdf.

Maxwell, K., Streetly, A. & Bevan, D. (1999) Experiences of hospital care and treatment seeking for pain from sickle cell disease: qualitative study. *British Medical Journal*, **318**, 1585–1590.

Morris, C.R., Barreda, F., Leibovich, S.A., Rutherford, M., Saulys, A., Stewart, M., Lavrisha, L., Vichinsky, E., Bell, M. & Treadwell, M.J. (2012) Quality improvement goals for sickle cell disease pain management in an urban paediatric emergency department: we can do better!. *Blood*, **111**, 2101.

Quinn, C.T., Rogers, Z.R., McCavit, T.L. & Buchanan, G.R. (2010) Improved survival of children and adolescents with sickle cell disease. *Blood*, **115**, 3447–3452.

Rees, D.C., Olujohungbe, A.D., Parker, N.E., Stephens, A.D., Telfer, P. & Wright, J. (2003) Guidelines for the management of the acute painful crisis in sickle cell disease. *British Journal of Haematology*, **120**, 744–752.

Sickle Cell Society (2008) Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK - 2018. Sickle Cell Society, London. Available from https://www.sicklecellsociety.org/sicklecellstandards/.

Singh, A.P., Haywood, C. Jr, Beach, M.C., Guidera, M., Lanzkron, S., Valenzuela-Araujo, D., Rothman, R.E. & Dugas, A.F. (2016) Improving emergency providers' attitudes toward sickle cell patients in pain. *Journal of Pain and Symptom Management*, **51**, 628–632.

Strickland, O.L., Jackson, G., Gilead, M., McGuire, D.B. & Quarles, S. (2001) Use of focus groups for pain and quality of life assessment in adults with sickle cell disease. *Journal of the National Black Nurses Association*, **12**, 36–43.

Tanabe, P., Hafner, J.W., Martinovich, Z. & Artz, N. (2012) Adult emergency department patients with sickle cell pain crisis: results from a quality improvement learning collaborative model to improve analgesic management. *Academic Emergency Medicine*, **19**, 430–8.

Whelan, C.T., Jin, L. & Meltzer, D. (2004) Pain and satisfaction with pain control in hospitalized medical patients: no such thing as low risk. *Archives of Internal Medicine*, **164**, 175–180.

Varni, J.W., Burwinkle, T.M., Seid, M. & Skarr, D. (2003) The PedsQL™* 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambulatory Pediatrics*, **3**, 329–341.

Wojciechowski, E.A., Hurtig, A. & Dorn, L. (2002) A natural history study of adolescents and young adults with sickle cell disease as they transfer to adult care: a need for case management services. *Journal of Paediatric Nursing: Nursing Care of Children and Families*, **17**, 18–27.

Worthington, R.L. & Whittaker, T.A. (2006) Scale development research: a content analysis and recommendations for best practices. *The Counseling Psychologist*, **34**, 806–838.