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Evaluating the feasibility of delivering a pain management programme for adults living with sickle cell disease

Rebecca McLoughlin, Red Cell Pain Management & Psychology Service, St George's University Hospitals NHS Foundation Trust, London, UK

Jenna Love, Cancer Psychological Support (CaPS) Team, St George's University Hospitals NHS Foundation Trust, London, UK

Jared G Smith, (1) Population Health Research Institute, St George's University of London, London, UK; (2) Clinical Research Unit, South West London & St George's Mental Health Trust, Springfield University Hospital, London, UK

Whitney Scott, Health Psychology Section, (1) Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (2) INPUT Pain management Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

Tim Noblet, Physiotherapy Department, St George's University Hospitals NHS Foundation Trust, London, UK

Correspondence: Rebecca McLoughlin, Red Cell Pain Management and Psychology Service, Phoenix Centre, Perimeter Road, St George's Hospital, Tooting, London, SW17 0QT Email: rebecca.mcloughlin@nhs.net.

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ORCID: Rebecca McLoughlin https://orcid.org/0000-0002-2910-1601

Jared G Smith https://orcid.org/0000-0001-6138-136X

Whitney Scott https://orcid.org/0000-0002-2529-9083

Tim Noblet https://orcid.org/0000-0002-7032-9966

Data sharing: The data that support the findings of this study are available from the corresponding author, upon reasonable request, to researchers who provide a methodologically sound proposal. Proposals should be directed to the corresponding author; to gain access, data requestors will need to sign a data access agreement.

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Abstract

Background

Pain is the prominent feature of sickle cell disease (SCD) and negatively affects quality of life. Delivery of pain management programmes (PMPs) has been suggested in clinical guidelines for pain management in SCD; however, further evidence of the feasibility and effectiveness of PMPs in this population is needed. This study explored the feasibility of delivering a sickle cell pain management programme (SCPMP) for adults within a haemoglobinopathies service.

Methods

A single arm, repeated-measures observational design was used to determine feasibility of delivering the SCPMP at one study site. Primary feasibility outcomes were recruitment, completion of treatment and outcome measures, satisfaction, credibility and acceptability to participants. Secondary feasibility outcomes were treatment outcomes and processes, frequency of vaso-occlusive crisis (VOC) and healthcare utilisation.

Results

Four of five feasibility criteria were met. Annual recruitment of eight participants to a SCPMP was not achieved. Twenty-nine people began a SCPMP during the study period. Twenty-five (86.2%) participants attended ≥ 5/8 sessions and 21 (84%) programme completers provided all end of programme questionnaires. Mean scores of > 7 on ten-point scales were seen across satisfaction and credibility questions. At least moderate (Hedge's g > 0.5) effect sizes were seen in pre-post SCPMP measures of pain interference, anxiety, depression, self-efficacy, pain-related worry and acceptance. A small (Hedge's g 0.4) effect size was seen in HRQoL. Following SCPMP attendance, mean frequency of self-reported VOC and hospital admissions reduced.

Conclusions

This study suggests that, given an adequate source of referrals, a SCPMP is feasible to deliver and appears acceptable and credible to participants. Exploration of influences on recruitment, such as barriers to group interventions, would be illuminating, prior to investigating feasibility of an adequately powered randomised-controlled trial.

Introduction

Sickle Cell Disease

Sickle cell Disease (SCD) is a debilitating, inherited blood disorder, the prominent feature of which is intense, fluctuating pain.[1] The term SCD describes a group of related disorders, characterised by the formation of 'sickle' or crescent shaped red blood cells on deoxygenation.[2] Sickled red blood cells lack flexibility, leading to haemolysis (reduced red cell life span) and haematological complications including vaso-occlusive crisis (VOC). VOCs are often unpredictable events associated with severe acute pain and potential for multisystem complications including stroke, retinal infarction, and acute chest syndrome.[3] Through the lifespan individuals with SCD face additional chronic complications, including organ dysfunction, which contribute to substantial morbidity, impaired health related quality of life and increased risk of premature mortality.[3, 4]

The experience of pain associated with SCD is the rule rather than the exception[5] and is the most common reason for hospitalisation.[2, 6] In addition to acute pain associated with VOC, persistent pain (also referred to as chronic or nociplastic pain) is a recognised feature of SCD.[7] The International association for the study of pain (IASP) defines chronic pain as pain that lasts or recurs for longer than three months.[8] Persistent pain in SCD has been described as pain that is present most days for at least six months in a single or multiple locations and may, or may not, be associated with contributing disease processes such as avascular necrosis.[6, 7, 9] In addition, Dampier and colleagues'[9] diagnostic criteria for chronic pain in SCD requires report of pain sensitivity on palpation or with movement, decreased range of movement, or weakness in the region of reported pain. Individuals with SCD may present with any combination of; acute pain, chronic SCD pain without contributory disease complication (alternatively described as primary persistent pain), chronic SCD Pain with contributory SCD complications (secondary persistent pain) or mixed chronic SCD pain.[8, 9]

Consequences of persistent pain in SCD include biopsychosocial impacts commonly experienced by individuals with primary persistent pain, including sleep disturbance, fatigue, activity restrictions and reduced health related quality of life.[9] Self-report data from adults with SCD shows high (27.6%) prevalence of significant depression and associations between depression, anxiety and daily pain (self-reported as 'not crisis pain') and poorer physical and mental health.[10]

In the UK, approximately 15,000 people who are predominantly of African and Afro-Caribbean descent live with SCD.[11] Therefore, individuals living with SCD also face the burden of health inequalities known to disproportionally impact Black, Asian and minoritised ethnic groups[12, 13] and are impacted by negative attitudes towards their condition which are often underpinned by racism.[14, 15] Evidence from the UK and USA demonstrates that negative and racist attitudes towards individuals with SCD can; impact adherence to guidelines for medication delivery,[16] underpin scepticism about severity of SCD related pain[15] and perpetuate perceptions that people living with SCD are 'drug seeking' and 'difficult', resulting in inadequate treatment and additional suffering.[15, 17] As a consequence, people living with SCD have described avoiding hospital due to lack of trust and difficult past experiences, placing additional burden on the individual.[15]

Historically, opioid analgesics have been the mainstay for managing acute and persistent pain in SCD.[4, 18] Opioid-based pain management addresses only the sensory/physical dimensions of pain and poses challenges including stigma,[4] opioid related risks, adverse effects, potential loss of efficacy over time and risk of opioid-induced hyperalgesia.[6, 7] The need for integration of non-pharmacological interventions has been identified to better address affective, behavioural, cognitive, cultural and social dimensions of pain.[4, 11, 18-20]

Pain Management Programmes

Pain Management Programmes (PMPs) have been described as the intervention of choice for people with persistent pain which adversely affects quality of life and significantly impacts physical, psychological and social function.[21] PMPs consist of a package of interventions delivered by a multidisciplinary team, typically within a group setting. The aim of PMPs is to increase functioning through the development of cognitive and behavioural self-management skills, rather than to directly reduce pain.[21-23] The largest body of research relates to PMPs utilising a traditional Cognitive-Behavioural Therapy (CBT) framework.[24] 'Third wave' cognitive-behavioural approaches including Acceptance and Commitment Therapy (ACT) and mindfulness based approaches are now

also incorporated into many contemporary PMPs.[25, 26] Systematic review and meta-analyses of CBT interventions for persistent pain, including PMPs, demonstrated small to medium effect size improvements on disability, mood and pain-related worry[24] thus supporting their routine implementation in clinical services. Additionally, group delivery of PMPs has social benefits and provides the opportunity to share experiences with others in similar circumstances, normalise pain experiences and address behavioural change and rehearsal in a natural social setting.[21, 27-29]

Despite the broad use of CBT within other pain populations, there remains limited evidence for CBT, including PMPs, for adults living with SCD. A single RCT evaluating group CBT for adults with SCD reported favourable differences in self-reported measures of coping and self-efficacy, immediately following the intervention.[30-32] A subsequent systematic review of psychological therapies for SCD[33] concluded that CBT may be useful for people with SCD but stated that efficacy/effectiveness remain unclear due to poor quality evidence. A feasibility study involving 22 young people with SCD (aged 16-24 years) showed improvement in self-efficacy following group delivery of the Stanford chronic disease self-management programme.[34] RCTs involving children and young people with SCD have investigated single session CBT training with smart-phone based home practice[35] and a family based CBT intervention[36], both with change in acute pain experience as primary aims.

Based on the low certainty of evidence from SCD and extrapolation of evidence from low back pain and fibromyalgia literature, clinical guidelines *suggest* that cognitive and behavioural strategies are delivered as part of a comprehensive SCD pain management plan.[11, 19] Interdisciplinary PMPs are identified as a potential method of delivery.[11] However, there is currently no evidence regarding the clinical application of these guidelines.

Aims and Objectives

Aim

To evaluate the feasibility of delivering an outpatient, group PMP to adults living with Sickle Cell Disease (SCPMP) and present preliminary outcomes.

Objectives

To evaluate the feasibility of delivering a SCPMP through:

i) Primary feasibility outcomes

a) analysis of rates of recruitment, and completion of treatment and outcome measures

b) assessment of credibility, satisfaction and acceptability of the intervention to participants

ii) Secondary feasibility outcomes

a) preliminary outcome estimates on treatment outcomes and process measures

b) preliminary data reporting healthcare utilisation and frequency of self-reported VOC

Methods

Design

A single arm, repeated-measures observational design was used. Treatment and data collection took place as part of routine clinical practice.

The study was reported in line with CONSORT guidelines for pilot and feasibility trials.[37] Where necessary, adaptations were made to reflect the aim of determining feasibility of delivering an intervention (rather than feasibility of trial design).[38] Ethical (REC Reference 14/NE/1069) and institutional approvals were obtained at the host site prior to the study.

Study setting

The SCPMP was delivered within an interdisciplinary pain management service staffed by a clinical psychologist (0.6 whole time equivalent) and specialist physiotherapist (0.4 whole time equivalent) both with more than ten years' experience in delivering interdisciplinary PMP's in specialist pain services and additional expertise in clinical haematology. The pain management service was situated within a multidisciplinary red cell and haemoglobin disorders unit which provides care for approximately 500 adults living with SCD, thalassemia and rare anaemias.

Participants

Participants were a consecutive sample of adults with SCD and persistent pain (pain lasting greater than 3 months[8]). Referrals were predominantly from the units' Consultant Haematologists. However, patients known to the service could self-refer for assessment and referrals **into the interdisciplinary pain management service** were accepted from Haematologists from other NHS Trusts. Potential

participants were assessed by the programme facilitators to determine suitability for the SCPMP using inclusion and exclusion criteria presented in Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
▪ Sickle Cell Disease (all genotypes; HbSS, HbSC…)
▪ Persistent pain (pain on most days for > 3 months) judged to be leading to significant physical disability and/or distress
▪ Age ≥ 18 years
▪ Motivated to attend weekly, group PMP
▪ Able to communicate within a group setting, with content delivered in English
▪ Able to attend suggested course dates
Exclusion criteria
▪ Unable to communicate within a group setting with content delivered in English
▪ Engagement in group anticipated to be impacted due to active, significant mental health problem (e.g., severe depression with suicidal ideation) or primary addiction problem
▪ Unable to attend PMP due to other commitment e.g., caring responsibility

Prior to attending the SCPMP, some participants completed individual pain management physiotherapy or psychology sessions due to clinical need judged at assessment. Haematological management of SCD continued throughout the SCPMP. Participants were allocated to programmes according to time of referral and ability to attend the course dates. Groups were not allocated based on demographic or other features. All participants provided written informed consent for their data to be used in this research prior to starting a SCPMP.

Sample size

We aimed to recruit 30 participants to the study, estimating recruitment of 7-8 participants from each of the first four programmes. Groups of 8-10 participants were considered optimal.[21] However, it was agreed that groups would run with a minimum of three participants, as ability to recruit to a SCPMP was unknown. Programme dates were not pre-determined.

A sample of 30 participants sits within the recommended range of 24 and 50 participants in feasibility studies to enable estimates of the standard deviation for use in sample size calculations for full-scale trials.[39, 40]

Intervention

The SCPMP ran as an eight session, outpatient group programme providing 36 hours contact time.[21] Additional group follow-up sessions, each lasting two hours, were provided at one, six and twelve months after the programme. (Please note: collection of data at twelve-month follow-up was not included in the original ethical approval and, therefore, was completed as part of routine clinical practice, but is not included in this study).

The SCPMP content aligned with guidelines for PMP's,[21] was grounded in CBT principles and integrated third wave CBT approaches, including values-based goal setting and mindfulness practice.[41] Adaptations to standard PMP content were made to reflect the nature of SCD with significant examples including; i) acknowledgement within 'impact of pain' discussions of the life-long, hereditary nature of SCD, impact of pain and treatment burden throughout the lifespan, and impact of negative and racist attitudes towards individuals living with SCD, ii) integration of acute pain mechanisms related to VOC within pain education discussions and iii) discussion of strategies for managing pain attributed to both VOC and 'flare-up' of persistent pain. Adaptations were agreed following discussion with a patient representative and pain management and haematology clinicians. Core themes introduced within the SCPMP are shown in Table 2. Session format (described in more detail in supplementary Table 1) remained consistent during the period of data collection.

Table 2. Core themes introduced within the 8 session SCPMP.

Week 1	Overview of programme, Impact of pain & CBT framework, Introducing Values & Goals.
Week 2	Pain mechanisms. Goal setting (individual goals).
Week 3	Activity cycles and pacing. Exercise and movement.
Week 4	Psychoeducation; thoughts and feelings (1).
Week 5	Communication (1). Individual review.

Week 6	Thoughts & Feelings (2). Communication (2).
Week 7	Managing increases in pain (1). Friends and family session.
Week 8	Managing increases in pain (2). Review of progress, future goals and maintaining changes.

Primary Feasibility Outcomes

Recruitment and treatment and questionnaire completion

During the study period, the following data were collected to enable calculation of robust estimates of recruitment and treatment and questionnaire completion:

Number of individuals:

i) referred for interdisciplinary pain management assessment
ii) considered appropriate for SCPMP
iii) enrolled on SCPMP
iv) who completed SCPMP, one-month and six-month follow-ups
v) who completed outcome measures at each timepoint

Credibility, satisfaction and acceptability

Credibility, satisfaction and acceptability of the SCPMP to participants was assessed on completion of the programme and at six-month follow-up. Questions were devised for this study with reference to the treatment credibility scale[42] and standardized measures proposed for back pain research.[43]

Participants completed additional open-ended questions identifying the most useful aspects of the intervention, changes they would suggest to improve the SCPMP, and behavioural changes resulting from SCPMP attendance.

Patients Global impression of change (PGIC)

At six-month follow-up, participants completed a modified version of the Patient's Global Impression of Change (PGIC).[44] Participants provided a single rating of 'perceived change (if any) in activity limitations, symptoms, emotions and overall quality of life' on a seven-point rating scale with

options ranging from ‘no change (or condition has got worse)’ to ‘a great deal better and a considerable improvement that has made all the difference.’

Secondary Feasibility Outcomes

Treatment outcomes

Participants completed standardised self-report measures at four timepoints; at the start and end of the SCPMP, and one-month and six-month follow-ups. Outcome variables, selected to align with IMMPACT recommendations,[45] were pain intensity and interference (Brief Pain Inventory; BPI)[46], Anxiety and Depression (Hospital Anxiety and Depression Scale; HADS)[47], and health related quality of life (EQ5D5L).[48]

Treatment processes

Self-report measures were also used to capture information about clinically relevant treatment processes; pain self-efficacy (Pain Self-Efficacy Questionnaire; PSEQ)[49] and pain-associated worry (Pain Catastrophising Scale; PCS)[50] for CBT and acceptance (Chronic Pain Acceptance Questionnaire-8; CPAQ-8)[51] for ACT. Mean baseline scores and internal consistency values of secondary outcome measures can be found in supplementary Table 2. All questionnaires, other than the CPAQ, showed acceptable or good internal consistency.

Self-reported frequency of VOC and healthcare utilisation

The frequency of painful VOC was self-reported by participants for the six-months prior to starting the SCPMP and the six-months between programme completion and the six-month follow-up. Electronic health records were used to calculate frequency of admissions and length of stay for the twelve-months prior to, and the twelve-months post, SCPMP attendance. Where participants were referred from another hospital trust, data was requested from that trust.

Feasibility criteria

A priori criteria determining feasibility of delivering the SCPMP were not specified as the service was newly commissioned at the start of the study period. Feasibility criteria were formalised during and following the data collection period as the specific service context was better understood.

Feasibility of delivering the SCPMP (in the context of the study site) was judged against the following criteria: 1) Ability to recruit a minimum of eight participants to a minimum of one programme per year, 2) Attendance at a minimum of 5/8 sessions, which was considered the minimum required attendance to be exposed to the PMP core themes, by ≥ 80% of participants, 3) Completion of end of programme questionnaires by ≥ 80% of programme completers, indicating feasibility of collecting robust outcome data , 4) Mean treatment credibility and satisfaction scores of greater > 5 on ten-point numerical rating scales (representing the midpoint of the scale or higher) 5) Observed within-group differences from pre-to-post SCPMP of at least moderate magnitude (Hedge's g ≥ 0.5), consistent with potentially clinically important changes, seen on at least some treatment outcomes and process measures (excluding pain intensity, as pain reduction is not an aim of PMPs).[21]

Collection and analysis of frequency of VOC, hospital utilisation and length of stay data was included because evidence of change in these domains was considered relevant to people living with SCD and service providers. However, change in these domains was not considered essential for the delivery of the SCPMP to be feasible, therefore, they were not included within feasibility criteria.

Data Analysis

Primary outcomes

Pre-intervention characteristics and baseline measures, referral, treatment and questionnaire completion rates, treatment credibility and satisfaction, and PGIC scores were described using means (SDs) or frequencies (percentages) according to the nature of the data. Comparisons of patient satisfaction levels between post-PMP and 6-month follow-up were administered using paired sample *t*-tests.

Secondary outcomes

Differences on pre-PMP/post-PMP outcome measures between SCPMP completers and non-completers and between those with and without follow-up data were assessed descriptively (with means/SDs) and formally compared using one-way analysis of variance (ANOVA) when the number of participants were sufficient. To evaluate whether treatment outcomes changed after attending the SCPMP, an intention-to-treat (ITT) analysis was conducted using linear mixed models (LMMs), which yield more accurate estimates of effect for repeated measures studies with missing data.[52] For each outcome, time (pre-PMP, post-PMP, one-month follow-up and six-month follow-up) was

included as a categorical variable with a random intercept and specified autoregressive/identity covariance structure (selected according to model fit indices). Parameter estimates were obtained using the restricted maximum likelihood method (REML), with post-hoc pre-to-post-PMP and pre-PMP-to-six-month follow-up treatment effect sizes (Hedges *g*) calculated using estimated marginal means (EMMs) accounting for covariance across repeated assessments. Effect sizes were classified as small (Hedge's g >0.2) medium (>0.5) or large (>0.8).[53] In addition, pairwise comparisons (paired sample *t*-tests for pre-to-post-PMP and pre-PMP-to-six-month follow-up) including only those patients who completed treatment were carried out and Hedges *g* calculated.

Comparisons concerning patient-reported painful crises and record-based healthcare utilisation in pre-PMP and follow-up periods were computed using paired sample *t*-tests or mid-*p* McNemar tests.[54] LMMs and corresponding Hedges *g* were estimated using transformed values where continuous (outcome) variables did not approximate a Gaussian distribution according to skewness and kurtosis estimates, with acceptable range being between -1 and +1 and -1.5 and + 1.5, respectively.[55] Bias corrected and accelerated (Bca) bootstrapping using 2000 replications[56] was employed in all other analyses. To control for potential Type I errors as a result of multiple outcome testing, the false discovery rate (FDR) approach was applied to within-group comparisons across standardised measures, with control set to 5%.[57]

Results

Demographics

Participants comprised mostly females with a wide variety of ages and multiple sickle cell genotypes (Table 3). Almost all participants were taking opioid medication to help manage their pain and the majority were receiving SC disease-modifying treatment, such as blood exchanges or transfusions. All but five patients had suffered from painful VOC in the last six- months; more than half had experienced four or more crises in that period.

Table 3. Socio-demographic and clinical characteristics data of patients with sickle cell disease (SCD) participating in the pain management programme (*n* = 29). Values are frequencies (percentages) unless otherwise stated.

Age (mean years (SD))	41.8 (10.6; range 25-72)
Female / Male	25 (86.2) / 4 (13.8)
Ethnicity	
Black or Black British - African	9 (31.0)

Black – any other Black background	8 (27.6)
Other – not stated	6 (20.7)
Black or Black British – Caribbean	5 (17.2)
White – any other white background	1 (3.4)
Employment status	
Employed/Student	15 (53.6)
Unemployed	11 (39.3)
Retired	2 (7.1)
Sickle cell genotype	
HbSS	19 (65.5)
HbSC	6 (20.7)
HbS-B+ Thalassemia	3 (10.3)
HbS-B0 Thalassemia	1 (3.4)
Exchanges	17 (58.6)
Transfusions	3 (10.3)
Hydroxyurea	3 (10.3)
SCD complications	13 (44.8)
Other (chronic) pain condition	9 (31.0)
Previous psychology or physiotherapy input	12 (41.1)
Medication for pain	
Opioids	28 (96.6%)
Paracetamol	26 (89.7%)
NSAIDs	15 (51.7%)
Anti-epileptics	7 (24.1%)
Most common pain sites	
Hips and/or lower limbs	25 (96.2%)
Upper limbs	17 (65.4%)
Lower back and/or buttocks	15 (57.7%)
Chest/Throat	8 (30.8%)
Painful Crises (n = 27)	
6-month frequency	
None	5 (18.5)
1-3	7 (25.9)
4-6	6 (22.2)

≥ 7	9 (33.3)
Pain crisis duration (average in days)	
0-2	5 (20.8%)
3-7	12 (50.0%)
≥ 8	7 (29.2%)
Severity of crisis pain (0-10 scale)	
≤ 7	6 (22.2%)
8-9	15 (55.6%)
10	6 (22.2%)

Note. HbSS denotes homozygosity for the sickle cell gene (HBB glu6val), sickle cell anemia; HbSC denotes heterozygosity for the sickle cell gene (HBB glu6val) and the haemoglobin C gene (HBB glu6lys), sickle-haemoglobin C disease; HbS-B thalassemia denotes heterozygosity for the sickle cell gene (HBB glu6val) and one of the B-thalassemia gene mutations; SCD complications included (but not limited to) acute chest syndrome, respiratory failure, pulmonary hypertension, splenectomy, cholecystectomy, avascular necrosis, osteomyelitis, and hepatic iron overload. Other (chronic) pain condition included endometriosis, migraine, osteoarthritis and (non-sickle cell-related) joint-related pain problems.

Feasibility

Table 4 shows the feasibility of delivering the SCPMP against criteria relevant to the study setting.

Table 4: Feasibility of delivering a SCPMP within a haemoglobinopathies service, judged against site specific criteria

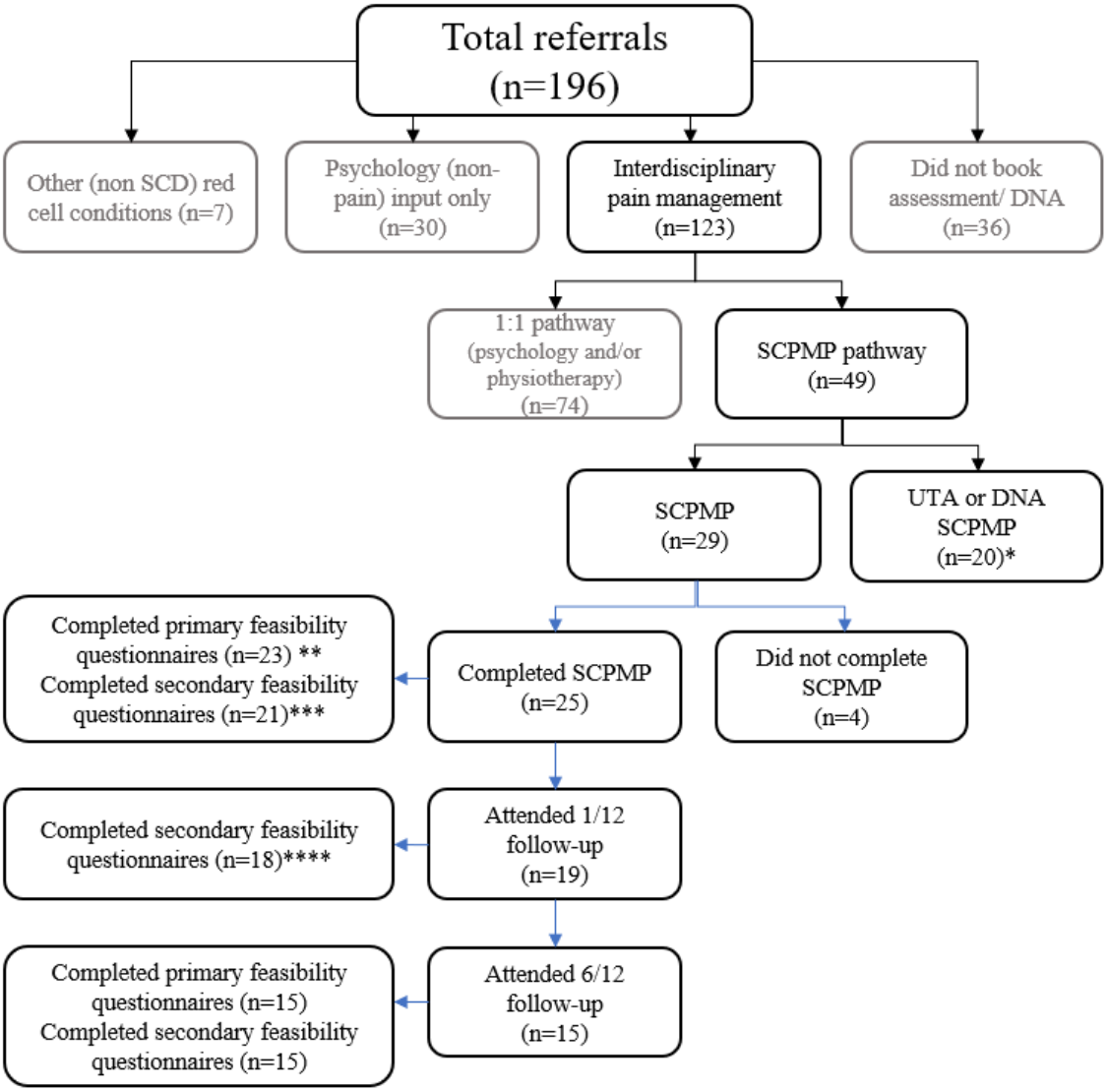
Feasibility Criteria	**Criteria met within study period.** (Yes/No)
1. Able to recruit a minimum of eight participants to a minimum of one SCPMP per year	No
2. Attendance at a minimum of 5/8 sessions by ≥80% of participants	Yes
3. Completion of end of programme questionnaires by ≥80% of programme completers	Yes
4. Mean treatment credibility and satisfaction scores > 5 on 0-9 scales (representing the midpoint of the scale or higher)	Yes
5. Observed within-group differences from pre-to-post SCPMP of at least moderate magnitude (Hedge's g ≥0.5), consistent with potentially clinically important changes, seen on at least some treatment outcomes and process measures (excluding pain intensity).	Yes

Recruitment, attendance and program completion

In total, 196 individuals were referred to the service during the study period, of which 123 people were (based on referral) appropriate for interdisciplinary pain management input and opted in for

an assessment (Figure 1). Following assessment, 49 (39.8%) people were invited to attend the SCPMP and of those people, 29 (59.1%) started a SCPMP.

Figure 1. Referrals to Red Cell Pain Management Service during study period

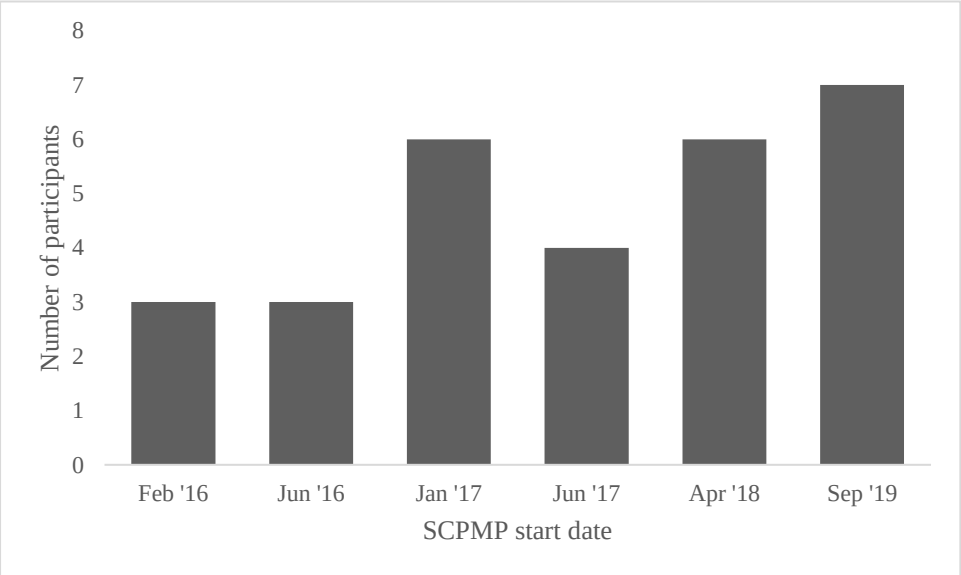


Note: DNA = Did Not Attend; UTA = Unable To Attend; 1/12 = follow-up 1 month after completion of SCPMP; 6/12 = follow-up six months after completion of SCPMP; * UTA/DNA SCPMP n=20 did not start the SCPMP during the study period and may have accessed 1:1 input, ceased involvement with the service or accessed the SCPMP after the study period; ** Primary feasibility questionnaires included credibility, satisfaction and acceptability scales and open-ended treatment experience questions; *** Secondary feasibility questionnaires included Brief Pain Inventory (Cleeland and Ryan, 1994), Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), EQ5D5L (Herdman et al., 2011), Pain Self-efficacy Questionnaire (Nicolas, 2007) Pain Catastrophising Scale (Sullivan et al., 1995), Chronic Pain Acceptance Questionnaire) (Fish et al, 2010); **** Nb. Primary feasibility questionnaires were not included at this timepoint.

Between February 2016 – June 2020, there were six SCPMP groups totalling 29 participants (Figure 2). Illness resulted in cancellation of one session, therefore, one SCPMP ran over seven sessions, not

eight. Recruitment was put on hold in March 2020 when individuals with SCD began shielding due to the COVID-19 pandemic. Participants in the final SCPMP group attended a remote six-month follow-up and submitted questionnaire responses electronically.

Figure 2. Recruitment to the SCPMP during the study period.



Across the six SCPMPs, 25 (86.2%) participants attended five or more of the eight SCPMP sessions. Of the four (13.8%) participants who did not complete the SCPMP, two dropped out after the first session and two dropped out after the third session. Of the 25 people who completed the SCPMP, the average participant attended 83.7% (range=62.5-100%) of intervention sessions (for those in the 7-session group (*n*=3), mean (*M*)=5.67 (81.0%), SD=1.16, range=5-7; for those in the 8-session groups (*n*=22), *M*=6.73 (84.1%), SD=1.20, range=5-8).

Twenty-three (92.0%) of the 25 SCPMP completers provided responses to primary feasibility questions at the end of the programme and 21 (84.0%) SCPMP completers, also provided secondary outcome questionnaires. Two participants completed treatment but did not complete measures at any point after treatment concluded. All other treatment completers completed measures at least on one occasion after the PMP. There was little to suggest that those who did not complete treatment and/or outcome measures were distinguishable from those who did. Scores on pre-PMP measures were highly comparable between those with any outcome data (i.e., those completing measures at some point after PMP participation; *n*=23) and those without (i.e., dropped out or did not complete measures; *n*=6), except for EQ-5D VAS (*M*(SD)=53.05 (18.87) vs. 67.80 (15.66), respectively) which suggested better perceived current health in those without outcome data, although the small *n* in this group precluded formal comparisons. Similarly, there were no significant differences on any pre-PMP or post-PMP (controlling for pre-PMP) measure between those with and

without outcome data at six-month follow-up (for all comparisons, *p*>0.053), suggesting missing outcome data was unlikely to be related to baseline pain-related and psychological function or the degree of change over the course of the PMP.

Acceptability, satisfaction and credibility of the intervention

In general, participants provided positive views with regards to acceptability, satisfaction and credibility of the intervention (Figure 3). All 23 SCPMP completers who rated the intervention's usefulness, the extent to which it met expectations of better pain management, and satisfaction in helping manage their pain, gave ratings of ≥ 5 on a ten point (0-9) numerical rating scale (where 0='not at all'/ 'not at all ok' and 9='very much so'/'totally ok'). Mean scores for each question were >7. These levels were comparable on the corresponding measures at six-month follow up (for each comparison, *p*>0.341). Participants were not quite as satisfied with their present symptoms post-PMP (M(SD)=5.00 (2.22), although there was a (non-significant) increase at six-month follow-up (M(SD)=6.33 (2.69); *p*=0.087).

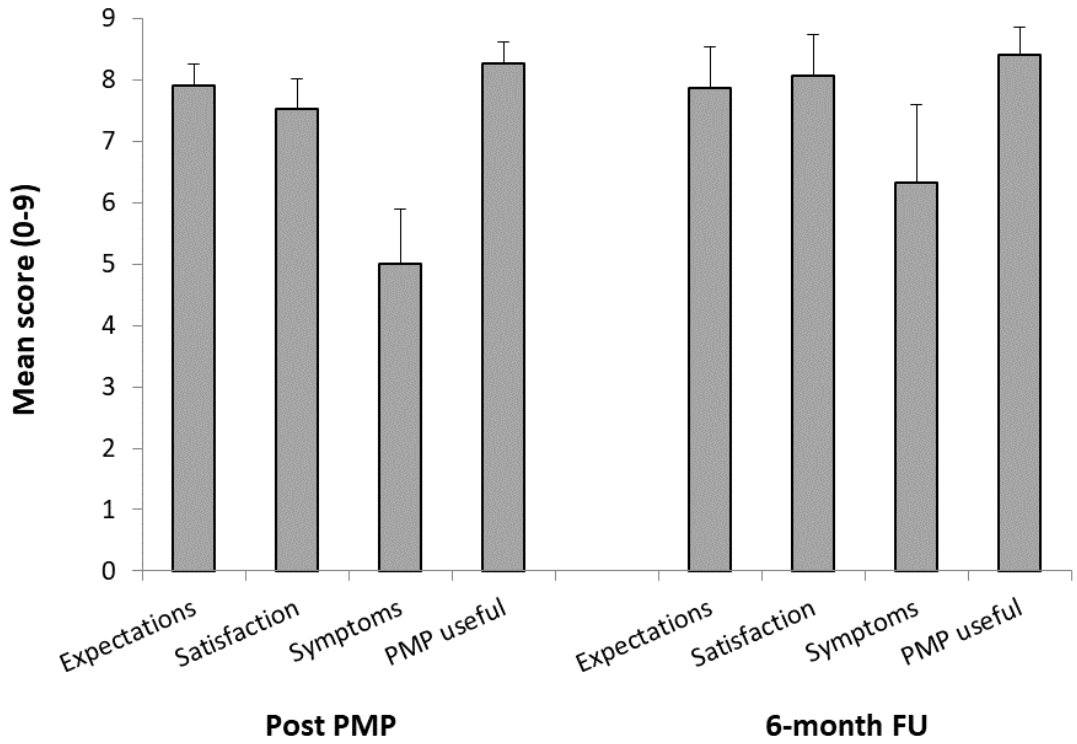


Figure 3. Acceptability, satisfaction and credibility of intervention at post-PMP (n=23) and 6 month follow-up (FU; n=15) according to meeting participants' expectations of better pain management

('Expectations'; 0 = 'Not at all', 10 = 'Very much so'), satisfaction that the treatment programme helps manage their pain ('Satisfaction'; 0 = 'Not at all', 10 = 'Very much so'), feelings about spending the rest of their lives with the present symptoms ('Symptoms'; 0 = 'Not at all OK', 10 = 'Totally OK'), and agreement that the PMP is useful for someone with sickle cell disease ('PMP useful'; 0 = 'Not at all', 10 = 'Very much so'). Error bars represent 95% confidence intervals.

The content analysis of open-ended treatment experience questions is shown in Supplementary Tables 3 and 4. On completion of the SCPMP, all respondents (n=23) identified various aspects of the intervention as useful with most responses including multiple useful elements. The most helpful aspects of the SCPMP were identified as increased understanding of pain and pain experiences (n=10, 43.5%), group aspects (n=4, 17.4.0%) and coping strategies/practical tips (n=4, 17.4%). Eleven (47.8%) participants stated that they would not change any aspect of the programme. The remaining participants made varied suggestions about changes they would make to the SCPMP, including hospital staff attending SCPMP sessions which was suggested by three (13%) participants. Nineteen (82.6%) participants identified at least one thing they were doing differently since attending the SCPMP, with pacing activity (n=5, 21.7%) and mindfulness practice (n=4, 17.4%) mentioned most frequently (Supplementary Table 3).

At six-month follow-up, 15 participants provided a broad range of responses to two open-ended questions (Supplementary Table 4). In response to the question 'What has the programme led you to think about, or do, differently?', four dominant responses were described; Pacing activity (n=6, 40.0%), exercise (n=5, 33.3%) and communication and altered perspectives (regarding pain) (both, n=4, 26.6%).

Participants' perception of global change

Fifteen participants completed the modified PGIC scale at six-month follow-up. Eight participants (53.3%) noted they felt better with a definite improvement that had made a real difference (one of these 'a great deal better'), while another two (13.3%) indicated that they were moderately better with a slight but noticeable change. Three participants (20.0%) responded that they were somewhat better, but that the change had made no real difference or a little better with no noticeable change, while another two participants (13.3%) suggested there was no change or hardly any change at all.

Treatment outcome and process measures

Table 5 shows the Estimated Marginal Means (EMMs) and main effects for treatment in linear mixed models on treatment outcome and process measures across pre- and post-PMP assessments and at one-month and six-month follow-ups. Participants significantly benefitted from the intervention across pain interference, anxiety and depression (treatment outcomes), as well as pain-related worry, acceptance and self-efficacy (treatment process) domains; differences across assessment periods were significant after controlling for multiple comparisons. There was less improvement in HRQoL and no change in pain severity, although HRQoL did show a medium (0.4) effect size improvement. Estimates of effect sizes for pre-to-post-PMP and pre-PMP-to-six-month follow-up indicated large improvements (>0.8) in pain-interference, anxiety, depression and pain self-efficacy and moderate (>0.5) benefits in pain-related worry and chronic pain acceptance. These effects were mostly maintained at 6-month follow-up, although the magnitude of (significant) treatment gains with respect to pain interference and depression was less pronounced. This pattern of findings was largely unchanged when considering the treatment completer sample (Supplementary Table 5).

Table 5. Estimated marginal mean values for SCD patients at pre-PMP, post-PMP, and 1-month and 6-month follow-ups (intention-to-treat analyses).

	Pre-PMP	Post-PMP	1-month FU	6-month FU		Pre-Post PMP effect size	Pre-6-month f/u effect size
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*p*	Hedge's *g*	Hedge's *g*
Brief Pain Inventory							
Pain Severity (0-10)	5.06 (4.47,5.64)	4.62 (3.95,5.29)	5.24 (4.53,5.96)	5.14 (4.37,5.90)	0.420	0.27	-0.05
Pain Interference (0-10)	**6.76 (6.02,7.50)**	**4.88 (4.02,5.74)**	**5.30 (4.37,6.23)**	**5.53 (4.52,6.55)**	**0.005**	**0.93**	0.60
Pain Self Efficacy (PSEQ; 0-60)	**24.72 (20.80,28.65)**	**34.79 (30.28,39.30)**	**34.10 (29.29,38.91)**	**34.90 (29.71,40.09)**	**<0.001**	**0.93**	0.94
Pain Catastrophising (PCS; 0-52)	**31.59 (27.12,36.06)**	**23.28 (18.40,28.16)**	**22.84 (17.59,28.08)**	**23.12 (17.08,29.15)**	**0.002**	**0.68**	0.69
Pain Acceptance (CPAQ; 0-48)	**17.79 (15.53,20.05)**	**21.16 (18.66,23.67)**	**22.45 (19.75,25.14)**	**21.22 (18.26,24.18)**	**0.015**	**0.54**	0.55
Mood							
Depression (HADS-D; 0-21)	**10.21 (8.74,11.68)**	**6.85 (5.22,8.48)**	**6.39 (4.69,8.10)**	**7.26 (5.41,9.10)**	**<0.001**	**0.80**	**0.72**
Anxiety (HADS-A; 0-21)	**12.86 (11.54,14.18)**	**8.86 (7.34,10.37)**	**9.51 (7.90,11.12)**	**9.19 (7.41,10.98)**	**<0.001**	**1.10**	**1.01**
Quality of life							
EQ Health (-0.285 - 1.000)	0.487 (0.388,0.586)	0.596 (0.484,0.707)	0.585 (0.467,0.702)	0.588 (0.463,0.713)	0.167	0.40	0.37
EQ VAS (0-100)	55.87 (48.73,63.01)	64.80 (56.92,72.67)	59.21 (50.87,67.54)	64.37 (54.44,73.30)	0.127	0.47	0.45

Note. PMP = pain management programme; FU = follow-up; PSEQ = Pain Self-Efficacy Questionnaire; PCS = Pain Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; EQ Health = EQ-5D-5L health state evaluation; EQ VAS = current overall health rating; CI = confidence interval. Significant effects are highlighted in bold. Positive effect sizes represent treatment benefit in corresponding measure.

Reported painful crises

Nine (64.3%) of the 14 participants who provided six-month follow-up data for self-reported frequency of VOC, reported a decrease in the number of painful crises experienced in the six-months post-SCPMP compared with that in the six-months prior to SCPMP attendance (three reported no change in frequency and two experienced increases). Excluding one outlier (who reported a decrease from 101 pre-PMP to 75 six-months post-PMP), the mean (SD) number of painful crises reported by patients in the periods before and after PMP participation numerically decreased from 4.62 (3.95) to 3.15 (2.67), but the difference was not significant (p=0.171). Pain severity of experienced VOC was comparable between pre- (M(SD)=8.65 (1.06)) and post-PMP periods (M(SD)=8.45 (1.34); p=0.502) as was the proportion of individuals with crises lasting 7 days or more (60% versus 50%; p=0.625).

Healthcare utilisation

Hospital admission data were available for 21 SCPMP completers. In the twelve-month period prior to SCPMP participation, the mean number (SD) of admissions was 2.00 (2.93). Admissions decreased significantly in the twelve-months post-PMP (M(SD)=0.81 (1.36); mean difference (95% CI)=1.19 (0.45,2.00); p=0.009). While nine (42.9%) of the participants had multiple admissions in the year prior to PMP attendance, only four (19.0%) did so in the year following completion. The three patients with high numbers (i.e.,> 5) of (annual) admissions pre-PMP all reduced admissions post-PMP by more than 40% (9-to-3, 9-to-5, and 7-to-3). Days in hospital (following admission; available for 20 participants) decreased from 10.65 (15.21) per patient in the 12-months prior to PMP attendance to 6.00 (11.27) in the period following PMP completion (mean difference (95% CI)=4.65 (1.50,8.32); p=0.038).

Discussion

This study aimed to explore the feasibility of delivering a group PMP for adults living with SCD. Feasibility was demonstrated on four of five criteria: 1) Completion of five or more SCPMP sessions by >80% of participants 2) completion of post SCPMP outcome measures by > 80% of programme completers, 3) Mean acceptability, satisfaction and credibility scores >5 on 10-point scales and 4) Moderate to large within group differences from pre-to-post SCPMP across treatment outcome and

process measures, except for HRQoL where effect size was small (0.4). However, during the study period, it was not possible to recruit a minimum of eight participants to a minimum of one SCPMP per year, therefore, this criterion was not met. These data show promise for the feasibility of delivering the SCPMP and provide guidance for how to further improve future delivery.

Primary feasibility aims

Following interdisciplinary assessment more than half (59.1%) of individuals assessed were offered 1:1 input, rather than the group PMP. It is not possible to identify when this decision was based on patient preference versus clinical judgement as reasons for 1:1 input were not collected. Potential influences on difficulties recruiting to the SCPMP could include the novel nature of this intervention within haematology services and lack of SCD specific evidence demonstrating effectiveness. Concerns about participating in a group may also have been a barrier to recruitment. Stigma associated with seeing a mental health provider or specialist has been reported within sickle cell literature[20] and could represent a barrier to attending a group intervention. Committing to a PMP in addition to existing medical appointments may have been an additional barrier for potential participants, as could predictions of difficulty attending due to frequency of VOC's and/or hospital admissions. Exploration of the impact of negative and racist attitudes towards individuals living with SCD could include examining the effect on engagement with services such as PMPs and would be a valuable area of future research. The factors impacting recruitment to the SCPMP cannot be elucidated from the data collected in this study. Therefore, future research exploring specific barriers and facilitators to group interventions in SCD would enhance understanding and strategies to address recruitment challenges. It also seems likely, based on these findings, that individual and group pathways that utilise cognitive-behavioural pain management approaches are needed to meet a diversity of patient need within this population.

Based on the ratios presented in this study, an average of 46 potential participants would need to be assessed to recruit 11 people per year to a SCPMP, which would bring attendance into optimum range when allowing for drop-out. **Although a small number of external referrals were received,** recruitment in this study came predominantly from one haematology service with an average referral rate of 31 potential SCPMP participants per year. **Developing pathways to promote** recruitment across regional haemoglobinopathies co-ordinating centres may represent a more feasible and efficient model, enabling programmes to run at optimum capacity. Issues relating to accessibility would, however, need to be considered. The SCPMP was modified for remote delivery during the COVID-19 pandemic (data is not included in this study) and remote delivery of PMPs has

been explored in chronic pain populations.[58, 59] Exploration of remote PMP delivery is warranted in SCD as this may increase accessibility and recruitment over larger geographical areas, although potential barriers presented by remote delivery for some participants, such as limited access to technology, would need to be considered.[58]

The feasibility targets of ≥80% of participants attending 5 or more sessions, and ≥80% of SCPMP completers submitting end of programme questionnaires, were achieved. The rate of attrition from the SCPMP was 13.8%. This compares favourably with rates of attrition across interdisciplinary PMP's which have been reported as ranging from 5%-46%.[60] Although this cannot be evidenced with the data collected, stringent assessment of suitability for a group PMP, and access to 1:1 input where indicated, may have contributed to the relatively low attrition rates. Of programme completers, average attendance was 83.7% (range 62.5% - 100%). Attendance at routine outpatient appointments is frequently cited as a challenge for adults with SCD, with published rates of attendance ranging from 47% to 77%.[61] SCPMP participants rated the programme as a credible intervention that met expectations, felt useful and was associated with high levels of satisfaction, which may have contributed to the relatively high attendance rates and supports the potential value of this intervention. Thus, despite challenges with recruitment, the current study suggests that once recruited, participants engaged with the treatment as intended and found it acceptable.

Secondary Feasibility Aims

Patient reported outcomes presented in this study must be interpreted with acknowledgement that this was not a controlled study, and the sample size was small. However, the preliminary data presented suggests that attendance at a SCPMP may positively impact pain interference, anxiety and depression, pain-related worry, self-efficacy, and pain acceptance, with improvements maintained at six months. The preliminary data presented also suggests that attendance at SCPMP may positively impact self-reported frequency of VOC, frequency of hospital admissions and length of stay. This is promising preliminary evidence which needs to be replicated in a larger sample, at other treatment centres and, optimally, using an RCT.

This study can inform future clinical practice and research to enhance inclusion of racialised and minority groups in pain research and treatment. This study describes delivery of the SCPMP in the context of a newly commissioned interdisciplinary pain management service. Delivery of the SCPMP continued during the study period with relatively small group sizes. This is significant because continued delivery of the SCPMP enabled the clinical team to develop relationships within the local SC community and increase trust. Letzen and colleagues[62] highlight that the mistreatment of

racialised individuals in science and healthcare settings undermines trustworthiness, therefore, trust must be earned through actions. Over time, SCPMP participants shared experiences of the programme in video reflections, at awareness events and during informal conversations which, anecdotally, contributed to increased credibility of the SCPMP locally. Whilst recognising that more can be done and committing to ongoing improvement, we acknowledge that strategies to enhance inclusion of minoritized individuals, specifically actions to build trust and increase community awareness, were integral to the delivery of the SCPMP during the study period. Inclusion of minoritised individuals within pain services and pain research may be enhanced through commitment to several key actions, as proposed by Hood et al [63]. These include but are not limited to, building trust; developing early, enduring and mutually beneficial collaborations with advocates and stakeholders from minoritised groups; reflecting on implicit bias; and, taking action to foster cultural humility within clinical and research teams[63].

Limitations

There are several limitations of this study beyond the small sample size and uncontrolled design. The repeated measures design may have resulted in measurement fatigue and the extensive battery of questionnaires may have represented a burden to participants. Outcome measures utilised in this study were selected to align with IMMPACT recommendations[45] to facilitate comparison across pain management literature but did not include collection of specific data relating to adverse events. Use of the treatment credibility scale[42] in its entirety would allow greater comparison with other feasibility studies. The measures selected did not include a sickle cell specific measure, such as the sickle cell self-efficacy scale (SCSES)[64] which should be considered in future studies to allow comparision across sickle cell literature. The appropriateness of the CPAQ for people with SCD should be ascertained before use in future studies, due to low cronbach's alpha for this scale in this study. Baseline data included self-report of medication use (classifed in broad groups, e.g. opioids). However, we did not collect these data at end of programme or follow-up. Collection of pre and post SCPMP opioid use could provide insight into the potential for a SCPMP to assist individuals in reducing opioid use, which can pose significant challenges for individuals living with SCD[7]. Collection of quantiative and qualitative data, enabling exploration of meaning and impact of medication changes for the individual, would be useful for future research. As this study was uncontrolled, observed improvements may be due to non-specific factors such as natural changes over time or

therapeutic relationships. However, the magnitude of observed effects across treatment outcome and process measures would appear unlikely in the absence of some type of treatment effect.

Conclusion

Findings from this study, including a small cohort of 29 participants, suggest that, with an adequate source of referrals, delivery of a SCPMP is likely feasible, the intervention is acceptable to participants and may positively impact pain related treatment and process outcomes and hospital utilisation. Given the paucity of evidence related to interdisciplinary PMPs for adults with SCD and the lack of inclusion of racialised and minoritised groups in pain research[65], this study provides valuable, real-life insights that can inform clinical practice and future research design. Evidence from this study suggests that exploration of potential barriers and facilitators of group work, and remote delivery of a SCPMP, both of which could facilitate recruitment, could be valuable areas of future research in SCD.

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Supplementary Table 1. SCPMP session format. Each weekly session comprised two core topics/ themes and additional aspects which were repeated each week including mindfulness practice, for example. Emphasis was placed on experiential learning and reflection, open discussion, and integration of learning into daily life through between session practice. Participants were encouraged to experiment with strategies during the group, for example, integrating movement into periods of sitting.

Approximate time (mins)	**Activity**
40	Introduction session (week 1)/ Reflection and review on content from previous session (weeks 2-8)
30	Mindfulness practice and enquiry
50	Core topic/ theme (e.g. pain mechanisms)
20	Break
60	Core topic/ theme (e.g. goal setting)
30	Movement practice
40	Plans for between session practice and personal values-based goal

Supplementary Table 2. Summary data and internal consistency of questionnaires and outcome measures for SCD patients at pre-PMP.

	Baseline (Pre-PMP)	
	Mean (SD)	Cronbach alpha (95% CI)
Brief Pain Inventory		
Pain Interference (0-10)	6.76 (1.71)	0.842 (0.735,0.916)
Pain Self Efficacy Questionnaire (PSEQ; 0-60)	24.72 (11.66)	0.914 (0.859,0.954)
Pain Catastrophizing Scale (PCS; 0-52)	31.59 (12.55)	0.928 (0.881,0.962)
Chronic Pain Acceptance Questionnaire (CPAQ; 0-48)	17.79 (6.83)	0.413 (0.015,0.691)
Hospital Anxiety and Depression Scale (HADS)		
Depression (HADS-D; 0-21)	10.21 (4.25)	0.810 (0.682,0.899)
Anxiety (HADS-A; 0-21)	12.86 (3.90)	0.782 (0.634,0.884)
Connor-Davidson Resilience Scale (0-100)	57.84 (18.03)	0.935 (0.892,0.966)
Multidimensional Scale of Perceived Social Support (0-7)	4.63 (1.61)	0.949 (0.916,0.972)

Note. SCD = sickle cell disease; PMP = pain management programme; SD = standard deviation; CI = confidence interval.

Supplementary Table 3: Content Analysis of open-ended questions on completion of SCPMP (n=23)

Q1. 'What did you find most useful about the SCPMP?'	**Q2. 'Was there anything that you would have liked to be different?'**	**Q3.'Is there anything that you will do differently now that the programme has finished?'**
Understanding pain (n=10)	Nothing/ No change (n=11)	Pace activity (n=5)
Group aspects (support, discussion, shared experience) (n=4)	Mixing some sessions to have both patients and healthcare professionals present (n=3)	Mindfulness (n=4)
Practical tips/ coping strategies (n=4)	Longer course (n=2)	Work towards goals (n=3)
Understanding/ managing cognitive and emotional aspects (n=3)	Longer friends and family session (n=2)	Notice/manage thoughts (n=3)
Prioritising/ being kind to self (n=3)	Discussion of cultural differences (n=1)	Communicate more about pain (n=3)
Listening to my body (n=3)	Discussion of expectations of a person with SCD from family (n=1)	Exercise or movement (n=3)
Pacing (n=3)	Planning more (n=1)	Look after/ prioritise myself more (n=2)
Communication (n=2)	Dealing with conflicts in hospital procedures and people (n=1)	Breathing exercises (n=2)
Friends and Family session (n=2)	More (physiotherapy) exercise or movement (n=1)	Live my life (despite pain) (n=2)
Exercise (n=2)	More time for mindfulness (n=1)	Try not to stop activity (due to pain) (n=1)
Mindfulness (n=2)		Try to worry less (about pain) (n=1)
Insightful topics included (n=1)		Delegate more (n=1)
Understanding/ managing stress (n=1)		Take time to relax (n=1)
Planning (n=1)		Review information given to refresh myself whenever I am feeling low (n=1)
Goal setting (n=1)		

Understanding Sickle Cell Disease (n=1)		
Having a flare-up box (n=1)		
Achieving goals and values (n=1)		
Detailed information (n=1)		
Breathing exercises (n=1)		
Reflection session each week (n=1)		

Supplementary Table 4: Content Analysis of open-ended questions at 6/12 follow-up session (n=15)

Q1. 'What did you find most useful about the SCPMP?'	**Q2. What has the SCPMP led you to think about, or do, differently?**
Understanding pain (n=3)	Pace activity (n=6)
Communication skills (n=3)	Exercise (n=5)
Management strategies (n=2)	Communicate more/ more effectively (n=4)
Goal setting (n=2)	Altered perspective/ attitude toward pain (n=4)
Pacing (n=2)	Ask for/ accept help when needed (n=2)
Managing cognitive and emotional aspects (n=2)	Plan more (n=1)
Altered perspective (n=2)	Take time out to care for me (n=1)
Input from facilitators (n=2)	Use medication earlier (n=1)
Weekly sessions (n=1)	Differentiate between acute pain and chronic pain (n=1)
Values (n=1)	
Group aspects (n=1)	
Learning to be kind to self (n=1)	
Exercise (n=1)	
SCPMP manual (n=1)	
Mindfulness (n=1)	
Relaxation techniques (n=1)	
Knowing I'm not alone with the feelings that I have (n=1)	

Supplementary Table 5. Mean values for SCD patients at pre-PMP, post-PMP, and 1-month and 6-month follow-ups (treatment completer analyses).

	Pre-PMP (n=29)	Post-PMP (n=21)	1-month FU (n=18)	6-month FU (n=15)		Pre-Post-PMP effect size	Pre-6-month f/u effect size
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*p*	Hedge's *g*	Hedge's *g*
Brief Pain Inventory							
Pain Average (0-10)	5.05 (1.26)	4.68 (1.54)	5.22 (1.51)	5.28 (2.21)	0.574	0.34	0.05
Pain Interference (0-10)	**6.76 (1.71)**	**4.87 (1.93)**	**5.25 (2.03)**	**5.48 (2.47)**	**0.021**	**1.04**	**0.74**
Pain Self Efficacy (PSEQ; 0-60)	**24.72 (11.66)**	**34.90 (9.30)**	**34.22 (11.28)**	**35.27 (8.39)**	**0.026**	**0.92**	1.11
Pain Catastrophising (PCS; 0-52)	**31.59 (12.55)**	**22.86 (11.73)**	**22.00 (10.44)**	**21.77 (13.18)**	**0.018**	**0.65**	0.60
Pain Acceptance (CPAQ; 0-48)	**17.79 (6.83)**	**21.48 (5.13)**	22.83 (4.63)	21.33 (6.52)	0.192	**0.48**	0.35
Mood							
Depression (HADS-D; 0-21)	**10.21 (4.25)**	**6.67 (3.57)**	**6.28 (3.59)**	**6.57 (3.52)**	**0.002**	**0.85**	**0.77**
Anxiety (HADS-A; 0-21)	**12.86 (3.90)**	**8.86 (3.53)**	**9.39 (2.66)**	**9.00 (3.70)**	**0.040**	**1.07**	**0.85**
Quality of life							
EQ Health (-0.285 - 1.000)	0.487 (0.283)	0.603 (0.269)	0.585 (0.249)	0.617 (0.209)	0.360	0.37	0.37
EQ VAS (0-100)	**55.78 (18.96)**	**62.81 (16.47)**	57.39 (20.14)	62.47 (18.36)	0.189	**0.57**	0.59

Note. PMP = pain management programme; FU = follow-up; PSEQ = Pain Self-Efficacy Questionnaire; PCS = Pain Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; EQ Health = EQ-5D-5L health state evaluation; EQ VAS = current overall health rating; CI = confidence interval. Significant effects are highlighted in bold. Positive effect sizes represent treatment benefit in corresponding measure.