Great Ormond Street Hospital for Children NHS Foundation Trust

NHS Health Research Authority

This protocol has regard for the HRA guidance and order of content

FULL/LONG TITLE OF THE STUDY

PIIPeR Trial: Impact of **P**aediatric **I**ntensive **I**nterdisciplinary **P**ain **R**ehabilitation for children with chronic pain and pain-related disability: Feasibility of recruitment to a randomised trial.

SHORT STUDY TITLE / ACRONYM

PIIPeR Feasibility Study

PROTOCOL VERSION NUMBER AND DATE

VERSION 3.0 22nd October 2025

RESEARCH REFERENCE NUMBERS

IRAS Number:	**343593**
SPONSORS Number:	**24NC06**
FUNDERS Number:	**Great Ormond Street Hospital Charity W1167C**

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Signed by: Neil Hubbard C5631BD2FC6A4C1... Date: 10-Nov-25

Name (please print): Neil Hubbard

Position: Head of Research Governance and Clinical Trials

Chief Investigator:

Signature: Suellen M Walker Date: 22/10/2025

Name: (please print): Suellen M Walker

LIST OF CONTENTS

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STUDY SUMMARY

Study Title	**PIIPeR Trial**: Impact of **P**aediatric **I**ntensive **I**nterdisciplinary **P**ain **R**ehabilitation for children with chronic pain and pain-related disability. Feasibility Phase to assess recruitment to a randomised trial.
Internal ref. no. (or short title)	**24NC06** PIIPeR Feasibility Study
Study Design	Single site randomised feasibility study Following referral and usual interdisciplinary assessment at Great Ormond Street Hospital Chronic Pain Clinic, children fulfilling eligibility criteria will be offered recruitment to a Paediatric Pain Rehabilitation Programme (PPRP) with randomisation to PPRP-Early (within 1-3 months of recruitment) or usual care until PPRP-Delayed (6-9 months post recruitment) Intervention • 3 week intensive PPRP delivered by an interdisciplinary team (clinical psychologists, physiotherapists, occupational therapists, advanced nurse practitioner, paediatric pain physicians) • daily timetabled sessions for participant and parent/carer(s)
Study Participants	Population • children and young people aged 11-18 years with chronic pain and significant pain-related disability
Planned Size of Sample (if applicable)	Feasibility study • 48 eligible participants recruited from paediatric chronic pain clinic over a 12-month period

Follow up duration (if applicable)	• PPRP-Early
	  ○ post intervention: 3 and 6 months post PPRP with completion of patient- and parent-reported outcome measures (PROMs)
	• PPRP-Delayed
	  ○ usual chronic pain clinic care and follow up until PPRP (review in pain clinic, completion of usual care PROMs and intermittent outpatient interventions)
	  ○ post intervention: 3 and 6 months post PPRP with completion of PPRP PROMs

Planned Study Period	2 years; proposed start date (pending approvals) September 2024
Research Question/Aim(s)	Primary Objective • assess feasibility of recruitment of children and young people (CYP) with chronic pain and pain-related disability to an intensive Paediatric Pain Rehabilitation Programme (PPRP) that includes randomisation to PPRP-Early (within 1-3 months) or usual pain clinic care until PPRP-Delayed (within 6-9 months) • results will inform design of ongoing PIIPeR Trial (10-year programme grant)

	Primary Outcomes: • proportion of eligible CYP referred to Chronic Pain Clinic who consent to enter the study • proportion of enrolled participants completing 3-week PPRP treatment • proportion of enrolled participants completing the 3 and 6 months post-PPRP assessment Secondary Outcomes: • completion rate for each of the study measures, including a range of validated patient- and parent-reported outcome measures (PROMs) and assessments of physical function • feasibility of calculating quality adjusted life years with Child Health Utility instrument 9 Dimensions (CHU-9D) • feasibility of calculating health and social care resource use and wider societal impact including days off school with Child and Adolescent Service Use Schedule (CA-SUS) • feasibility of capturing adverse effects • acceptability of study design Exploratory outcomes: • differences between the 2 randomised arms at 6-9 months: quality of life following intervention (Peds-QL 6 months post PPRP-Early) versus 'control' (usual care prior to PPRP-Delayed) • longitudinal pre-post intervention change in patient- and parent-reported outcome measures (PROMs)

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Great Ormond Street Hospital Children's Charity 40 Bernard St London WC1N 1LE **Phone**: (+44) (0) 20 3841 3841 **Email**: Grants@GOSH.ORG	

ROLE OF STUDY SPONSOR AND FUNDER

SPONSOR

Great Ormond Street Hospital NHS Foundation Trust will act as Sponsor and provide research governance oversight throughout the study. All research staff involved in the study will hold GOSH honorary or substantive contracts and will complete and maintain: Good Clinical Practice; Consent in Children training; and mandatory NHS and Trust training, including information governance and data

protection modules. Clinical staff delivering the PPRP intervention are employed by GOSH, and will also complete and maintain mandatory NHS and Trust training modules.

FUNDER

The PIIPeR Trial was funded in response to a Commissioned Call for a Programme Grant from Great Ormond Street Hospital Charity. The submission, review and award of the funding application has been administered by the GOSHC Grants team. Regular meetings co-ordinated by GOSHC with the Chief Investigators and representatives from relevant GOSH departments have overseen appointment of a project manager, refurbishment of space for the programme, and recruitment of PPRP research and clinical personnel.

The 10-year PIIPeR Programme Grant encompasses:

- the initial 2-year feasibility study proposed here (24NC06; IRAS 343593)
- results of the feasibility study will inform the design for ongoing follow-up and recruitment throughout the remaining period of the PIIPeR Programme Grant. An updated protocol will be developed and submitted to GOSH Research Governance review, NHS Research Ethics Committee and HRA for review.
- a parallel observational longitudinal cohort study is also funded within the PIIPeR Programme Grant. Paediatric Chronic pain Clinic Longitudinal Cohort (**PiCCoLO**): IRAS 340388; R&D No 24PC03; REC reference 24/WS/0048 (reviewed by West of Scotland Research Ethics Service); HRA Approval 3 June 2024. This study does not alter usual care and aims to:
    - recruit 8-18 year old CYP referred to Great Ormond Street Hospital Chronic Pain Clinic to collect baseline data, and usual clinical care data for participants who do not fulfil eligibility criteria for PPRP or who decline recruitment/randomisation to PPRP
    - retrieve data from medical history: baseline demographic and clinical data; patient- and parent-reported outcome measures (PROMs) completed as part of usual care at pain clinic assessments; treatment throughout clinical care pathway (usual duration 2 years)
    - option to consent/decline contact for longer-term video/online follow-up at 2 and 5 years post referral

The Sponsor and Funder will not be directly involved in the conduct of the study and will not influence the analysis or interpretation of data, or publication and dissemination of results.

CLINICAL TRIALS UNIT

UCL Priment CTU staff will be contribute to trial management, data management, reporting and oversight of adverse events, statistical and health economic analyses, and interpretation and potential publication of study results for the 2-year feasibility study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

PIIPeR External Advisory Group

An External Advisory Group will be co-ordinated by the funder (Great Ormond Street Hospital Charity) to oversee the full PIIPeR project and extension beyond the Feasibility Phase. Reports will be received from the Trial Steering Committee. Members will include:

- Prof Navil Sethna, Clinical Director, Pediatric Pain Rehabilitation Center, Boston Children's Hospital (External Advisor)
- GOSH Divisional representative (Operation and Images) who will also provide a reporting line to the GOSH Executive.
- GOSHCC representative (link to GOSHCC Advisory Board)
- Research/statistical advisors as appointed by GOSHC
- Prof Tonya Palermo, Center for Child Health, Behaviour and Development, Seattle Children's Hospital (Trial Steering Committee Chair)
- PIIPeR Investigators: Dr Glyn Williams, Prof Suellen Walker, Prof Chris Eccleston

PIIPeR Trial Steering Committee

The Trial Steering Committee will provide overall supervision of the trial, will review the reports and recommendations of the TMG and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the Sponsor. Members will include:

- Prof Tonya Palermo, Center for Child Health, Behaviour and Development, Seattle Children's Hospital (Trial Steering Committee Chair)
- Dr Helen Laycock, Clinical Lead, Pain Management Service, Great Ormond Street Hospital
- PIIPeR Investigators: Dr Glyn Williams, Prof Suellen Walker, Prof Chris Eccleston
- Patient/public representative to provide input relevant to patient experience and review progress with recruitment, patient/family satisfaction, and input/advice for further research protocols and applications.
- Statistics Advisor (to be identified by Priment CTU)

The Steering Group will meet 6-monthly to review progress with patient recruitment and data collection. More frequent meetings will be held if requested by the Sponsor. The clinical and research teams will provide reports on an annual basis, and as requested by the Steering Group.

Trial Management Group

The TMG will be administered by Priment CTU and will include the Chief Investigator and Priment trial staff. The group will meet regularly (approximately 4 times per year). The TMG will review recruitment figures, time from recruitment to entry into PPRP(Early) or PPRP(Delayed), duration of attendance throughout the 3-week programme, and feasibility and acceptability of the study design reported by participants, parents, and clinical staff. The TMG will also review and discuss any adverse events. Members will include:

- PIIPeR Investigators: Dr Glyn Williams, Prof Suellen Walker, Prof Chris Eccleston
- Priment Clinical Trials Unit staff
- Representatives from the PIIPeR Research Team (postdoctoral research associate and/or research nurse) and the PIIPeR Clinical Team to report on progress and feedback to their other team members.

Patient & Public Involvement

- A patient/public representative will join the Trial Steering Committee and provide input relevant to patient experience, review progress with recruitment, patient/family satisfaction, and provide input/advice for further research protocols, and dissemination of results.
- The PIIPeR postgraduate research associate (Dr Anna Fieldwalker) has had initial meetings with the Great Ormond Street Young Peoples Advisory Group. Further presentations and meetings are planned to discuss ongoing aspects of the trial, gain feedback and advice regarding data collection, and develop methods for effective dissemination of reports and anonymised results in formats of interest to CYP and the public.
- Throughout the feasibility study, participants and parent/carer(s) will complete measures related to:
    - acceptability of the study design and randomisation
    - satisfaction with the intervention

PROTOCOL CONTRIBUTORS

FUNDER: REVIEW AND DEVELOPMENT OF PROGRAMME GRANT

The PIIPeR Programme Grant (10-year) was reviewed by the GOSHC Research Assessment Panel. An initial feasibility trial to assess a randomised design was suggested, and a randomised trial within cohort design was developed following discussion with Clinical Epidemiology at UCL GOS Institute of Child Health. While improving the quality of evidence for a paediatric intensive interdisciplinary pain programme is important for ensuring long-term sustainability of the intervention, it is also acknowledged that randomising CYP with significant disability, emotional distress, and poor school attendance to usual care alone or a waiting list control group can raise ethical issues and practical management challenges. Therefore, the proposed design was chosen:

- randomisation to PPRP(Early) versus PPRP(Delayed) to ensure CYP who fulfil eligibility criteria and agree to enter the study can access the intervention
- all children continue usual pain clinic care with intermittent outpatient interventions until entry into PPRP
- patient outcomes 6 months following PPRP(Early) are compared to outcomes after a similar time period prior to PPRP(Delayed)

Input from a Clinical Trials Unit and their involvement in the initial 2-year feasibility phase was also recommended. The subsequent revised Programme Grant underwent external peer review, responses to the reviewer comments were submitted, the protocol was presented to and reviewed by an External Advisory Committee set-up by GOSHC, and the programme was funded.

CLINICAL TRIAL UNIT

UCL Priment CTU have contributed to the current protocol and will be involved in the conduct and management of the PIIPeR Feasibility study. Staff included in protocol development include: *Priment Trialist*: Irwin Nazareth; *Statistician*: Baptiste Leurent; *Clinical Trials Operations*: Anne Marie Downey and Sharon Forsyth, *Health Economist*: Rachael Hunter and Abdinasir Isaaq; and *Priment Data Manager*: Sven Nelson.

KEY WORDS: chronic pain; children; adolescents; paediatrics
interdisciplinary treatment; pain management

STUDY FLOW CHART

A: **PIIPeR FEASIBILITY: Recruitment and Participant Groups**

Site: **GREAT ORMOND STREET HOSPITAL** PIIPeR Feasibility Trial					
Baseline		**Chronic Pain Clinic Assessment**			
		UC	**Fulfil eligibility criteria for PPRP** PPRP Staff Assessment		
			Consent to Randomisation		Decline
1-3 mths				**PPRP (Early)**	**PPRP (Decline)**
3 mths		UC	UC	3mth FU postPPRP	UC
6 mths		UC	UC	6mth FU	UC
6-9 mths			**PPRP (Delayed)**		
9 mths			3mth FU postPPRP		
12 mths			6mth FU		
Subgroups		**Grp A**	**Grp B**	**Grp C**	**Grp D**

Groups:

Grp **A** = patients not reaching pain and disability inclusion criteria or have exclusion criteria; continue with intermittent outpatient management (Usual Care, UC)

Grp **B** and **C** = meet PPRP criteria and consent to PPRP and randomisation; Grp **C** PPRP (Early) within 1-3 months versus Grp **B** PPRP (Delayed) within 6-9 months

* *flexibility in entry scheduling required: family requirements; 10 programmes per year*

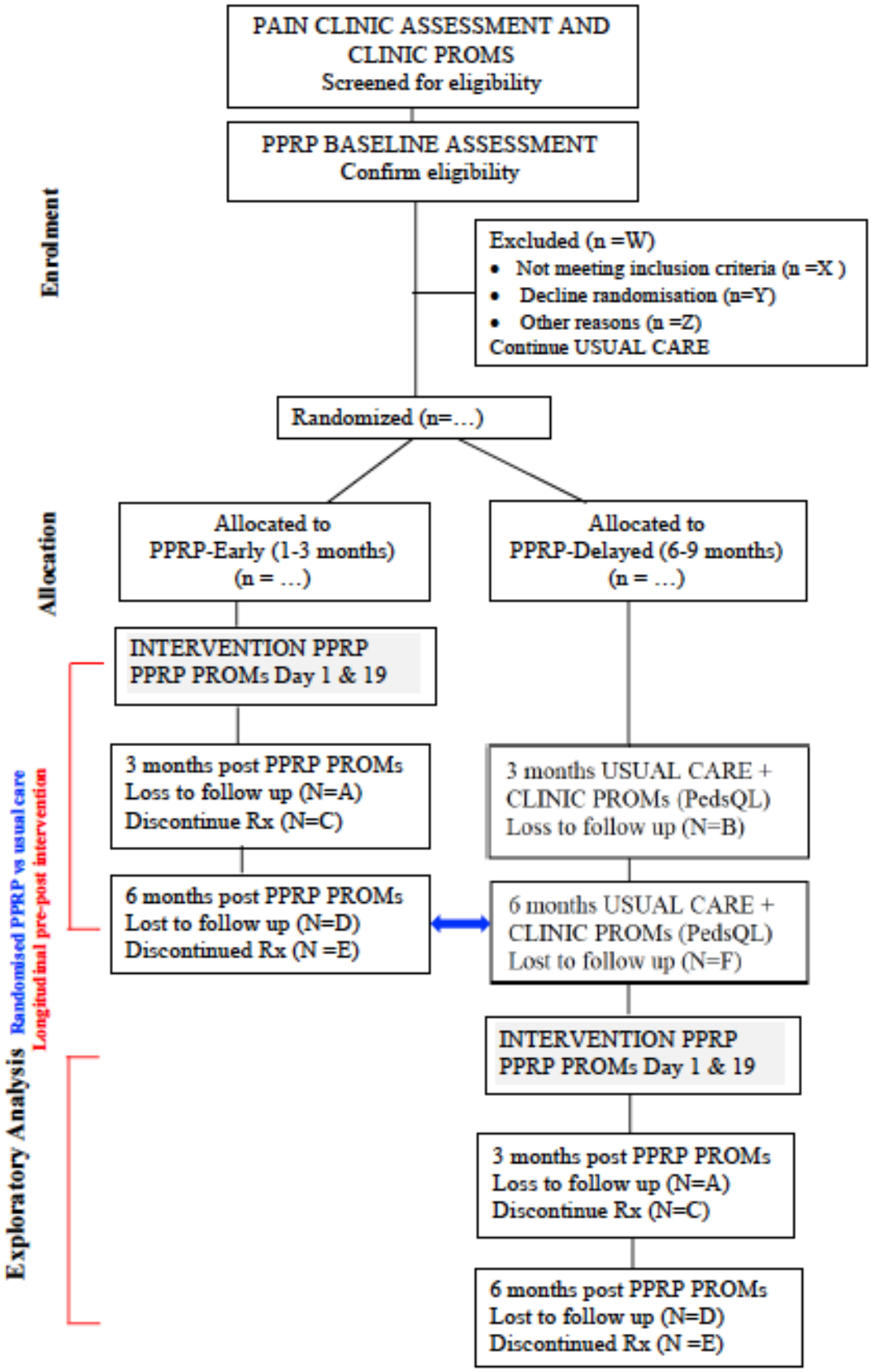
Grp **D** = fulfil eligibility criteria for PPRP but patient/family decline entry into the trial and PPRP due to family choice, social circumstances, do not wish to consent to recruitment and/or to randomisation. The number of patients declining PPRP will inform the feasibility of the randomised design (see Section 7 Trial Design). Reasons for declining will be documented. These patients will continue usual pain clinic care.

Feasibility Analysis Groups

(i) proportion of referred patients fulfilling eligibility criteria [(B+C+D) / (A+B+C+D)]
(ii) proportion of eligible patients consenting to randomisation [(B+C) / B+C+D)]
(iii) proportion entering PPRP within randomised timeframe [PPRP(Early); 1-3 months post recruitment] or PPRP(Delayed); 6-9 months
(iv) proportion completing follow-up at 3 and 6-months post PPRP

Legend*:* UC, usual care (intermittent outpatient interdisciplinary care); PPRP, Paediatric Pain Rehabilitation Program (intensive day-patient interdisciplinary care); FU, follow-up including patient- and parent reported outcome measures (PROMs)

B: PIIPeR FEASIBILITY: Participant Flow



Feasibility Analysis

Primary outcome

(i) proportion fulfilling eligibility criteria

(ii) proportion of eligible consenting to randomisation

(iii) proportion completing 3 and 6-months post PPRP follow-up

Secondary outcomes (both arms combined)

(i) data collection: Day 1 and Day 19 PPRP; 3 and 6-month follow-up

(ii) programme delivery and attendance

(iii) adverse events

Exploratory Analysis

- group differences in PedsQL-Child between the 2 randomised arms
- longitudinal within-patient pre-post intervention change in PPRP PROMs in both arms

Legend:

CLINIC PROMs = Pain intensity; PedsQL-Child; PCS-Child; PI-ED; PedsQL-Parent, HADS, PCS-Parent

PPRP PROMs = CLINIC PROMs plus additional measures

See APPENDIX 2 for SCHEDULE OF EVENTS

STUDY PROTOCOL

PIIPeR Trial: Impact of **P**aediatric **I**ntensive **I**nterdisciplinary **P**ain **R**ehabilitation for children with chronic pain and pain-related disability. Feasibility of recruitment to a randomised trial.

1 BACKGROUND

1.1 Chronic pain in children and young people

In England, 17.8% of children and young people (CYP) aged 11-15 years self-report chronic pain at multiple body sites; a prevalence that is similar to other European countries and Canada.[1] More significantly, 5-6% of CYP experience more intense moderate-severe chronic pain that adversely effects physical and emotional function, quality of life, and school attendance, and requires increased use of health care.[2,3]

Chronic pain requires a biopsychosocial formulation as multiple physiological, psychological, social and family factors contribute to the experience and maintenance of chronic pain and pain-related disability.[4] Interdisciplinary management typically includes medical and nursing care, physiotherapy and psychology interventions, and patient/parent education.[5]

There are socio-economic inequalities in access to paediatric chronic pain services in the UK.[6] The COVID-19 pandemic exacerbated pre-existing limited or delayed availability of specialist care,[7,8] and further highlighted the need for biopsychosocial assessments of public health needs. Effects on the presentation and impact of chronic pain have increased the need for interdisciplinary care:

i. emergence or worsening of chronic pain associated with exacerbation of physical or mental conditions (e.g. poor sleep, inactivity, anxiety and fear);[9]
ii. impact of lock-down and isolation on CYP and family psychosocial function and perceived benefits and harms from school closures;[10,11]
iii. acute viral illness or COVID-related syndromes acting as a trigger for chronic pain conditions[12] and/or potential long COVID symptoms in CYP (e.g. chest pain, headaches, fatigue, muscle weakness).[13]

Effective management of chronic pain in CYP with pain-related disability is relevant to broader areas of NHS concern. Childhood obesity is associated with chronic pain and functional disability, and will benefit from improved physical function during PPRP. Despite limited efficacy, opioids may be prescribed for CYP with chronic pain, particularly when access to specialised services is limited. Ineffective medications are reduced and substituted with self-management strategies during PPRP. As childhood pain can influence health-related outcomes throughout the lifespan, improving patient and parental understanding and self-management has generalisable benefits for managing chronic pain in adulthood**.**

1.2 Current Practice at GOSH Pain Clinic

The Chronic Pain Clinic at Great Ormond Street Hospital (GOSH) is one of the largest UK paediatric pain clinics and one of few nationally commissioned services. Patients present with moderate-severe chronic pain that is difficult to manage.

Interdisciplinary treatment approaches are considered the gold standard for effective management of chronic pain in CYP.[5,14] The current standard of care at GOSH chronic pain clinic incorporates assessment by an interdisciplinary team (pain physician/paediatrician, clinical nurse specialist, physiotherapy, psychology), followed by a biopsychosocial formulation and management plan that

is discussed with the child and family.[4,15] Usual management encompasses pain education sessions, medication (if indicated) and/or non-pharmacological techniques such as TENS, psychological interventions and physiotherapy with a home exercise program. Management is delivered and progress reviewed via intermittent outpatient appointments (face-to-face and online Pain Clinics) plus telephone follow-up (each patient has a named pain nurse specialist as their primary contact). The care team liaise with local care teams, and with the child's school and social services as required.

As part of **usual care**, the impact of chronic pain at baseline and changes at subsequent clinic appointments are assessed and monitored with a range of patient- and parent-reported outcome measures (PROMs). This includes measures of pain intensity, quality of life (PedsQL Child and Parent Versions), emotional distress (Pediatric Index of Emotional Distress; Hospital Anxiety and Distress Scale for Parents) and catastrophizing about pain (Pain Catastrophizing Scale Child and Parent Versions). Improvements in quality of life (reflected by a higher PedsQL total score, range of 0 to 100, mean±SD 84±15 in health CYP[16]) have been documented with our usual care (pre score at referral: 47.3 ± 19.7; post score at discharge: 61.9 ± 21.2; *n* = 63). However, there is significant variability at both timepoints. and for CYP with severe pain-related disability, gains with this intermittent approach can be slow and/or inadequate. The proportion of patients achieving a PedsQL total score of 66 (defined as a clinically significant cutoff[17]) reveals the following: 16% maintained PedsQL score > 66 at both time points; 37% improved to scores >/= 66; but 48% did not attain cutoff of 66.

Access to usual care by specialist outpatient interdisciplinary paediatric pain management services is limited. Referrals to GOSH Pain Clinic are received from London (39%), the South East (31%) and East of England (25%), with the remainder (6%) from across England and the UK.[6] For many CYP ongoing care by local services is required, but resources and expertise vary widely. In particular, specialist physiotherapy and child and adolescent mental health services can be difficult to access or unavailable for chronic pain management. As a result, potential gains can be delayed for many months, resulting in more prolonged pain-related disability, emotional distress and poor school attendance.

1.3 Intensive interdisciplinary pain rehabilitation programme for CYP and parent/carer(s)

CYP with high levels of functional disability may be refractory to intermittent outpatient interventions. In such cases, co-ordinated management by an interdisciplinary team (psychology, physiotherapy, occupational therapy, medical, nursing) within an intensive pain rehabilitation programme aims to improve progress toward developmentally appropriate goals (e.g. educational attainment, independent living).

Compared to usual care with repeated outpatient visits over several months, intensive PPRPs at other international centres have delivered more rapid and enhanced return to function, that is sustained for longer periods.[18-20] Patients benefit from direct involvement with all members of the team, and progress is closely monitored. Improved function is the primary treatment focus, with a shift to self-management of pain, and improvement in mood, coping strategies and activities of daily living.[17] The group dynamic and shared experience is also beneficial for CYP and families who have been isolated and/or have received very mixed information regarding pain and appropriate management. Importantly, a PPRP encompasses **family-centred care** and also includes education, skills and interventions for parent/carer(s).[17,21]

In adolescents with chronic pain (mean pain duration 4 years; mean absence from full-time education 17 months) improvements in physical function and reductions in disability and anxiety following a 3-week interdisciplinary paediatric pain rehabilitation programme (PPRP) were first reported in 2003.[22] Subsequent studies across different practices settings and countries have documented benefits following PPRP, including reductions in disability and improved school participation[14,20,23-27] that are maintained at 4-5 year follow-up.[17,24,28,29]

1.4 Components of Intensive interdisciplinary Pain Programme

a) Pain Education

AIM: to provide child/family with explanation of differences between acute and chronic pain; emphasize non-protective nature of chronic pain; principles that guide biopsychosocial interventions; improve understanding of pain neuroscience (sensitisation, plasticity, sensory and emotional aspects of pain, endogenous control); risk-benefit of medications; medical support to reduce reliance on ineffective or inappropriate medications and interventions.

Many children referred to a chronic pain clinic have experienced pain for years. Parental distress associated with an inability to achieve relief for their child's pain often leads to repeated medical assessments and investigations.[30] While appropriate for acute management pathways, multiple consultations can result in families receiving a wide range of opinions and explanations regarding the cause, management, and likely time-course of chronic pain. This component of the intervention will allow the child and the family to gain a fuller understanding of the chronic pain.

b) Psychological assessment and interventions

AIM: to identify and reduce maladaptive thoughts and behaviours; improve coping strategies and self-management; improve sleep patterns

Emotional function, mood (anxiety and depression) and pain coping style (pain catastrophising, approach/avoidance) influence chronic pain experience.[31] Passive coping contributes to the increased disability associated with high levels of pain-related anxiety.[32-34] By contrast, positive expectations about one's ability and the responsibility to exert control over the pain are protective of normal functioning.[35] Therefore, in addition to reducing maladaptive cognitions and behaviours, identifying and targeting factors that improve participant and parental resilience can also improve outcomes.[36] Systematic reviews report significant reductions in pain and disability with psychological therapies for CYP with chronic pain.[21,37,38] In relation to potential treatment mechanisms, improvements in pain catastrophizing and self-efficacy predicted changes in pain intensity and functional disability following an intensive interdisciplinary intervention for CYP with chronic pain.[39]

c) Physical therapy

AIM: encourage regular exercise and movement despite pain; minimise fear-avoidance and misconceptions regarding pain indicating 'damage'; improve strength and flexibility to achieve functional goals

Pain captures attention and elicits fearful thinking about pain.[40] While reduced activity and protective measures are appropriate for acute pain, catastrophic appraisals and avoidance behaviours can increase pain-related disability in chronic pain conditions.[35,41] Co-ordinated delivery of active physical therapies within an interdisciplinary framework that incorporates goal-setting, pacing of activities and addressing pain-related fear of movement aligns with current recommendations,[5,14,42] and can be effectively delivered within a PPRP.

d) Occupational therapy

AIM: maximise independence in age-appropriate activities of daily living, self-care, and family activities; reduce co-morbidities (sleep hygiene; graded return to school)
Chronic pain[43] and anxiety[33] can disrupt normal developmental trajectories with negative effects on adolescent social development ('independence', 'emotional adjustment' and 'identity formation')[44] and long-term educational and vocational attainment.[45] School attendance is a major functional and social outcome for CYP. Chronic pain diverts attention,[46] increases anxiety related to school function and attendance,[47] and increases school days missed (2.8x that associated with asthma).[48] Sleep disturbance is a common comorbid symptom, and has been linked with pain intensity, physical and functional disability, and mood disturbance.[49] Improved sleep patterns following PPRP[50] correlated with reduced disability,[51] and predicted longer-term benefit in global and school,[49] and progress toward developmentally appropriate goals (e.g. school completion, independent living).[17]

e) Parent support and skills training

AIM: reduce parent distress; learn self-management skills to assist child following discharge; shift parent attention and behavioural responses towards encouraging function despite pain.
Parental pain-related attitudes, behaviours and perceptions influence the child's functional disability.[52] Parents with higher catastrophic thoughts prioritise their child's pain control over activity engagement.[53] In addition, parental perceptions may under- or over-estimate child report, and while concordance between child-parent tends to be high for physical function, it is often lower for emotional function and internalised symptoms.[54-58] Parental problem-solving skills training improves parental mental health and catastrophising, and reduces their child's anxiety.[52,59] Psychological interventions for parents can improve parenting behaviour (reduce maladaptive or solicitous behaviours) and parental mental health.[21]

1.5 Efficacy of Interdisciplinary Interventions for CYP with chronic pain

Systematic reviews have utilised different inclusion criteria to assess evidence for interdisciplinary interventions in CYP with chronic pain. While within-group improvements have been noted in pre and post intervention outcomes, the quality of current evidence was low.[60,61]

Liossi et al, 2019[60]

- 28 eligible studies (interdisciplinary treatment co-ordinated by 2 or more health professionals, delivered for variable duration in inpatient or outpatient setting)
  - 19 studies had a single group pre-post design
  - 9 classified as randomised trials, but utilised different outcomes with variable follow-up
- between-group meta-analysis for patients randomised to interdisciplinary interventions versus control/comparison (placebo, waiting list, single disciplinary intervention)
  - significant reductions in pain intensity at 0-1 month (4 RCTs)
- within group pre-post intervention trials showed significant improvements in:
  - pain intensity immediately post-intervention (11 studies including 4 RCT) maintained to 12 months (4 studies including 2 RCTs)
  - functional disability immediately post-intervention (10 studies, including 2 RCTs) maintained at 3 months (3 studies, 1 RCT)
  - reduced anxiety at 3 (3 studies, 1 RCT) and 12 months (2 studies, 1 RCT)
  - reduced pain catastrophising immediately (5 studies, 2 RCT) and 3 months (3 studies, 1 RCT).
- reported limitations and low quality evidence from between-group analyses due to:
  - inclusion of heterogenous chronic pain populations
  - standardising 'usual care' is difficult, and blinding is not possible

- variability in outcome measures utilised
- characteristics and delivery of interventions varied across centres

Claus et al, 2022[61]

- 13 eligible studies (interdisciplinary team with 1 to 4 week programme of inpatient or day-stay treatment)
  - within group pre-post design: one RCT (immediate post-intervention), 12 non-randomised longitudinal
- within-group improvements at 12-month follow-up
  - large improvements in mean pain intensity, disability and school attendance
  - moderate improvements in anxiety and depression
  - perceived parental financial burden (1 study) and health care cost reduced (1 study)
- reported limitations resulting in very low to low certainty of evidence
  - high risk of bias and heterogeneity between studies
  - imprecision in outcome measurement and no studies evaluated the impact on quality of life.

1.6 Evidence Gaps

Quality of Evidence

To improve the quality of evidence, additional randomised controlled trials are recommended with: more detailed reporting; a range of validated core outcomes; robust and longer-term follow-up; and pre-registered protocols.[60,61] However, it is also acknowledged that additional funding and research infrastructure is required,[61] and randomising CYP with significant disability, emotional distress, and poor school attendance can raise ethical issues and practical management challenges.[5,20] Additional evidence is also needed to determine the most effective components and to confirm the cost-effectiveness of PPRPs.[5,60]

Health care and family costs

A recent systematic review (15 studies evaluating cost-of-illness, and 10 studies with economic evaluations) concluded that: i) chronic pain in CYP is associated with substantial direct and indirect costs; ii) specialised pain treatment for CYP can reduce overall costs; and iii) failure to include indirect costs in most studies may lead to an underestimation of the financial burden of paediatric chronic pain.[62]

In 2005, the mean cost per UK adolescent with chronic pain was estimated at £8,000/year, with an overall cost-of-illness to UK society of approximately £3.84 million/year.[63] In addition to direct health care costs, there are 'hidden' economic impacts related to parental time off work for care and hospital visits for CYP.[63] In 2014, paediatric pain-related conditions in the USA were associated with health care expenditures of $11.8 billion.[64] To date, evaluations of psychological interventions have focussed on clinical utility and efficacy rather than cost-effectiveness.[65] For pharmacological interventions, the lack of evidence-based guidelines[66] can result in multiple agents (e.g. anti-convulsants, opioids, over-the-counter medications) being trialled and/or continued despite limited efficacy, and unrelieved pain and sleep deficiency in adolescents have been associated with increased risk of subsequent prescription opioid misuse.[67-69] In the US, reductions in emergency room visits and inpatient stays in the year post- versus pre-interdisciplinary paediatric chronic pain care reduced hospital costs by $36,228/patient/year.[70] In Germany, reductions in analgesic prescriptions and hospitalisations, and a shift to more goal-focussed outpatient psychotherapy was identified from 1-year pre to 1-year post PPRP[71] and

progressive reductions in hospitalisations and overall health care cost in the first and second years following intensive interdisciplinary pain treatment.[72]

2 RATIONALE

PIIPeR Trial (Programme Grant): Hypothesis

For children and young people (CYP) with chronic pain and significant pain-related disability, co-ordinated management in an intensive interdisciplinary rehabilitation programme, that incorporates individual and group-based interventions (i.e. physical, psychological, occupational therapy and medical management), parental education and family-centred care, will improve quality of life, reduce pain-related disability and improve progress toward developmentally-appropriate goals (e.g. educational attainment, independent living).

Questions

1. In CYP with chronic pain and significant pain-related disability does PPRP have a greater impact on quality of life than usual intermittent outpatient care?
   - randomised trial of PPRP(Early) versus PPRP(Delayed)
   - comparison: PedsQL-Child total score (primary outcome) 6 months following PPRP(Early) *versus* usual care prior to PPRP(Delayed)

2. Does an intensive PPRP produce sustained improvements in function for CYP with chronic pain?
   - longitudinal cohort with pre versus post intervention assessments and regular follow-up (3, 6 and 12 months, 2 and 5 years)
   - comparison: trajectory of change in patient-reported outcome measures (quality of life, emotional function, coping style), physical function, educational/vocational milestones, health care utilisation

PIIPeR Feasibility: Hypotheses

1. Recruitment to a study evaluating an intensive interdisciplinary paediatric pain rehabilitation programme (PPRP) that incorporates randomisation to early entry into the PPRP (within 1-3 months of recruitment) or usual care until deferred/delayed entry into the PPRP (6-9 months following recruitment) is feasible and will be acceptable to CYP and parents.

2. It is feasible to deliver a standardised interdisciplinary programme, and participants and parent/carers will attend sessions throughout a 3-week programme.

3. It is feasible to collect patient- and parent-reported outcomes (PROMs) that assess multiple domains of pain-related disability, and health care/family costs, at several timepoints (first and last day of 3-week intervention, 3 and 6 month follow-up).

3 THEORETICAL FRAMEWORK

The concepts that frame this study are:

- Moderate-severe chronic pain in CYP adversely effects physical and emotional function, quality of life, school attendance and educational attainment, and requires increased use of health care.[2,3]
- CYP with high levels of functional disability may be refractory to intermittent outpatient interventions. Co-ordinated management by an interdisciplinary team within an intensive pain rehabilitation programme has delivered more rapid and enhanced return to function, that is sustained for longer periods.[18-20]
- Chronic pain in CYP is associated with significant direct costs associated with health-care utilisation and indirect impacts on family finances (e.g., parental time off work to care for the child).[63,64]
- To improve the quality of evidence, additional randomised controlled trials are recommended with: more detailed reporting; a range of validated core outcomes; robust and longer-term follow-up; and pre-registered protocols.[60,61]
- Randomising CYP with significant disability, emotional distress, and poor school attendance can raise ethical issues and practical management challenges,[5,20] and acceptability by CYP, parent/carers and clinical pain teams requires evaluation.
- Additional evidence is needed to determine the most effective components and to confirm cost-effectiveness of PPRPs.[5,60]

The current proposal is an important first step for evaluating the feasibility and acceptability of randomising CYP to the intervention at different time points. This allows a randomised comparison of outcomes following PPRP (6 months following PPRP-Early) versus usual clinical care (prior to PPRP-Delayed). While an early intervention may more rapidly reduce pain-related disability, engagement in an intensive programme may be improved following a period of usual care that allows participants and families to become more familiar with a biopsychosocial formulation of chronic pain. The current proposal addresses this question, and aims to maximise the number of eligible CYP who can access the intervention.

While centres in Europe and the United States have identified reductions in healthcare utilisation following PPRP, evaluating cost-effectiveness in the UK is necessary to support future sustainability in the NHS.

Results of the feasibility study will inform study design and protocols for ongoing recruitment to the PPRP with longer-term follow-up (2-5 years) throughout the remaining period of the PIIPeR Programme Grant.

4 RESEARCH QUESTION/AIM(S)

The overarching aim of the PIIPeR Trial is to evaluate the impact of an intensive interdisciplinary paediatric pain rehabilitation programme (PPRP) that incorporates physiotherapy, psychological, occupational therapy and medical interventions for CYP with chronic pain and significant pain-related disability. A feasible and acceptable study design is needed to assess the degree and duration of benefit for psychosocial and physical function, school attendance and family function, and provide evidence of cost-effectiveness.

4.1 Objectives

The current proposal will evaluate the feasibility and acceptability of recruitment to a randomised trial in this patient population. We will focus on the following objectives:

- research design feasibility: recruitment and randomisation
- intervention feasibility: attendance and delivery
- collection of detailed data sets: Case Report Form (CRF), participant- and parent-reported outcome measures (PROMs) and physical assessments at several time-points (first and final day of PPRP, 3 and 6-month follow-up)
- quantification of health care utilisation and family costs
- identification of adverse effects: frequency, type, severity

4.2 Outcomes

Primary Outcome

- feasibility of recruitment, randomisation, and follow-up
    - proportion of CYP referred to GOSH Pain Clinic who fulfil eligibility criteria for PPRP and consent to participate in a randomised study of PPRP(Early) versus PPRP(Delayed)
    - proportion of enrolled participants for who it was feasible to enter the PPRP within the designated time-frame
    - proportion of enrolled participants completing the 3-week PPRP
    - proportion of enrolled participants who completed the 3 months and 6 months post-PPRP assessments

Secondary Outcomes

- intervention feasibility and delivery
    - attendance by participant and parent/carer throughout 3-week PPRP ('dose received')
    - proportion of patient and parent programme sessions delivered according to timetable and manuals for planned interventions 'dose delivered'),
        - deviations, reasons and potential contributing/mitigating factors recorded
        - number of essential elements delivered ('dose delivered')
    - acceptability of study design
        - 0-10 Numerical Rating Scale (0=completely unacceptable, 10=completely acceptable)
        - participant, parent/carer, Pain Clinic care team, PPRP clinical care team
    - participant and parent-reported global impression of change and satisfaction

- feasibility of collecting data that encompasses clinical history, demographic data, patient- and participant reported outcomes (PROMs)
    - proportion of complete datasets: Case Report Form, PROMs and questionnaires, and physical assessments
    - timepoints: Day 1 and Day 19 of PPRP; 3 months and 6 months post-PPRP

- feasibility of collecting and analysing health care and family/societal costs
    - calculation of health and social care resource use and wider societal impact including days off school, with Child and Adolescent Service Use Schedule (CA-SUS)
    - calculation of quality adjusted life years with Child Health Utility instrument 9 Dimensions (CHU-9D)

- identification and reporting of adverse events and negative effects
    - log of type, severity, impact on PPRP attendance, management

Exploratory outcomes

- group differences in PedsQL-Child total score between the 2 randomised arms at 6-9 months post recruitment
    - 'active arm': 6-month follow-up after PPRP(Early)
    - 'control arm': follow-up after usual care prior to entry into PPRP(Delayed)
- longitudinal within-patient pre-post intervention change in PROMs (*primary*: PedsQL-Child and PedsQL-Parent total scores) in both arms
    - time points: Day 1 PPRP; final Day 19 PPRP; 3- and 6-month follow-up

5 STUDY DESIGN and METHODS OF DATA COLLECTION AND DATA ANALYIS

5.1 POPULATION

CYP aged 11-18 year-old referred to GOSH Chronic Pain Clinic with chronic pain (>3 months duration) and fulfil eligibility criteria for significant pain-related disability.

5.2 INTERVENTION

Usual Care: At all Chronic Pain Clinic appointments, patient and parent-reported outcome measures are completed as part of usual care. This includes measures incorporated in the eligibility criteria (CLINIC PROMs: PedsQL-Child, PI-ED and PCS-Child and parental versions PedsQL-Parent, HADS, PCS-Parent). Participants will continue usual care until entry into PPRP. Participants randomised to PPRP(Delayed) will continue intermittent outpatient interventions with regular follow-up, completion of PROMs, and review of progress at Chronic Pain clinic appointments. Medication use will be based on the clinical assessment by the pain physician and clinical nurse specialist as part of usual pain clinic care prior to entering the PPRP. Dose, efficacy and side-effects will be monitored at follow-up, and medications with limited benefit or side-effects will be weaned and ceased, in line with usual pain clinic care. Prescribed and over-the-counter medication use prior to the intervention and at 3 and 6-month follow-up in Pain Clinic will be recorded in the Participant's medical records and CRF.

A range of times for entry into the intervention (i.e. 1-3 months for PPRP-Early and 6-9 months for PPRP-Delayed) increases flexibility of scheduling according to family preference/availability and availability of places within PPRP. Any significant participant or family factor (e.g. major exams, or family illness) that precludes entry within this designated timeframe will be discussed on a case-by-case basis, and the reason will be documented in the medical records and the CRF. The family will be offered dates across a wider timeframe but as close as feasible to the randomised time window. This will ensure that eligible participants who have already provided consent/assent are not denied access to the intervention.

Intensive Interdisciplinary Paediatric Pain Rehabilitation Programme (PPRP)

The PPRP comprises 3-weeks (Monday to Friday, 9.30am-4.30pm) of intensive interdisciplinary management. Participant, parent/carer and joint sessions are delivered by **interdisciplinary staff** (pain physician, advanced nurse practitioner, psychologist, physiotherapist, occupational therapist) with complementary skills working together to provide consistent information and interventions within a structured timetable.
A standardised timetable for activities during the PPRP intervention has been developed (*see Appendix 4*). This encompasses group and individual sessions and activities for patient/participant(s) and parent/carer(s). Manuals will include details of the content for standardised delivery. The structure and content of the intervention is based on current best evidence,[5,14] and reported efficacy from similar paediatric programmes.[17,18,22-24,28,29,52,74,75]

Graded activities, education, and skills for self-management aim to reduce pain-related disability and achieve sustained benefit. Rather than receiving separate sessions specifically dedicated to the individual components (e.g., physical therapy, psychological therapy, occupational therapy), all components are delivered in a combined interdisciplinary manner using the following themes:

- DISCOVER (e.g., learning about change and readiness, fear avoidance);
- EXPLORE (e.g., relaxation techniques, goal setting);
- DO (e.g., pacing, practical skills/outings, mindfulness activities);
- MOVE (e.g., learning about pain cycles, physical activity);
- REVIEW & PREPARE (e.g., planning for the future, relapse management).

Each week of the programme involves an overarching theme of:

- ONBOARDING (Week 1; education and introduction to themes)
- CONSOLIDATION (Week 2; practice learned ideas), and
- SELF-MANAGEMENT (Week 3; progress toward independent skills).

See: **APPENDIX 4 PPRP TIMETABLE**

5.3 OUTCOME MEASURES

5.3.1 Feasibility and Acceptability Outcomes

Feasibility of recruitment

- Screening and Recruitment Log (maintained and securely stored by research team)
- record the number of participants/families who:
  - are referred to GOSH Pain Clinic and fulfil eligibility criteria
  - attend baseline assessment with PPRP clinical team
  - agree to discuss trial with research team
  - provide parental consent and child assent/consent
  - randomised and enter into PPRP(Early) or PPRP(Delayed)
  - begin intervention within proposed time frame: PPRP(Early) 1-3 months or PPRP(Delayed) 6-9 months
    - any diversions from these time periods and associated significant reasons will be recorded in the medical notes and CRF
  - decline or subsequently withdraw from the trial (and reasons if given)
  - lost to follow-up (reasons if given, contact attempts and dates).

Intervention feasibility and fidelity

- proportion of enrolled CYP and parents completing 3-week PPRP
  - attendance by participants and parents ('dose received - exposure') and their opinion ('dose received - satisfaction') will be collected with questionnaires and interviews
- programme delivery and treatment fidelity
  - proportion of patient and parent programme delivered according to timetable and manuals for planned interventions (treatment fidelity)
  - audio or video recordings of randomly selected sessions assessed by independent raters for performance according to protocol (number of essential elements delivered; 'dose delivered'), and protocol deviations[73]

Data collection

- proportion of complete datasets at each time point
  - Day 1 PPRP (immediate pre-intervention); Day 19 Final Day PPRP (immediate post-intervention); 3- and 6-month follow-up
  - Case Report Form (incorporates clinical history, demographic data)
  - patient- and participant reported outcomes (PROMs) completed on REDCap

- CASUS and CHU-9D for collecting health care and family/societal costs

Acceptability of study design

- scores from 0-10 Numerical Rating Scales (0=completely unacceptable to 10=completely acceptable) of study that includes randomisation to PPRP(Early) or PPRP (Delayed) completed by:
  - participant and parent/carer
  - usual clinical care team referrers in Chronic Pain Clinic
  - PPRP clinical staff

Adverse events / negative effects

- adverse events reported to PPRP clinical staff during the programme that preclude engagement with planned sessions or activities and lead to withdrawal from the PPRP will be recorded in the Adverse Event Log
- negative effects reported by participants and families (qualitative interview) will be documented in the Negative Effects Log

5.3.2 PPRP Participant and Parent-Reported Outcome Measure (PPRP PROMs)

Patient- and parent-reported validated questionnaires that encompass the core outcome set for paediatric chronic pain trials[76] will quantify changes in pain-related disability, quality of life, mood, physical function and school attendance for CYP with chronic pain.

These will be collected at 4 time points: Day 1 PPRP (immediate pre-intervention); Day 19 Final Day PPRP (immediate post-intervention); 3- and 6-month follow-up. Questionnaires will be self-completed in a REDCap database.

Child Report

- ***** *Pain Visual Analogue Scale (VAS)*: comprises 3 VAS scores for the child's pain, over the previous week: Pain score now, average pain score (over last 7 days), worst pain score (over last 7 days). Higher scores indicate increased pain.
- ***** *Paediatric Quality of Life Generic Core V4 (PedsQL, Child)* for CYP aged 8-12 or 13-18 years. Twenty-three items cover four domains: physical, emotional, social, and school function.[77,78] Higher scores (range 0-100) indicate normal function, with values of 84±15 reported in health CYP.[16,78] Clinical thresholds associated with minor, moderate, and major paediatric chronic conditions are total scores of 78, 76, and 70, respectively.[79]
- ***** *Pain Catastrophizing Scale (Child [PCS-C])* includes 13 items (domains: magnification, helplessness, rumination), and is validated for children 9-17 years.[80-82] In children, catastrophising is a significant predictor of pain, functional disability, and health-related quality of life.[83] Scores range from 0-52, with 0-14 reported by healthy controls, 15-25 ranked as moderate catastrophising, and scores over 20 commonly reported in chronic pain populations.[84,85]
- ***** *Paediatric Index of Emotional Distress (PI-ED)* comprises 14 anxiety and depression items and has been validated for 8-17 years of age.[86] The maximum score is 42, and a threshold of 20 indicates risk of developing comorbid anxiety and depression.

*** measures also completed at clinic visits (CLINIC PROMs) as part of usual care**

- *PROMIS(R) (Patient-Reported Outcome Measurement Information System) Pain Interference Scale* assesses pain-related interference with daily living over 8 items using a 5-point Likert Scale, with scores ranging from 8 (low interference) to 40 (high interference).[87,88]
- *PROMIS(R) Sleep Disturbance* assesses difficulty around sleep with 8-items measured using a 5-point Likert scale, with scores ranging from 8 to 40; higher scores denote increased sleep disturbance.[87,88]
- *Emotional Approach Coping 8* (EAC-8): measures emotional processing and emotional expression.[89] This 8-item measure using a 4-point Likert scale, with scores ranging from

8 to 32, with higher scores indicating more adaptive emotional coping.[89] Pain specific emotion regulation predicted pain outcomes at 3-month follow-up.[90]

Parent-report

- ***** *Pain Visual Analogue Scale (VAS)*: Parental report of the child's pain: Pain score now, average pain score (over last 7 days), worst pain score (over last 7 days).
- ***** *Paediatric Quality of Life Generic Core V4 Parent Report (PedsQL-P)*. Parents report their child's quality of life across the same physical, emotional, social, and school function domains.
- ***** *Pain Catastrophizing Scale (Parent [PCS-P]* relates to thoughts and feelings of the parent/carer when their child is in pain.[81]
- ***** *Hospital Anxiety and Depression Scale (HADS)* measures anxiety and depression in adults,[91] and parents report thier own feelings. Scores for 14 items range from 0 to 21 for each scale (0-7 normal function; 8-10 mild; 11-14 moderate; 15-21 severe anxiety/depression.[92] UK normative data includes >6000 participants.[93]
  *** measures also completed at clinic visits (CLINIC PROMs) as part of usual care**
- *Bath Adolescent Pain – Parental Impact Questionnaire (section 6)*.[94] Eight items with the stem ''in the last two weeks living with my child in pain I have...'' reflect the impact of the child's chronic pain on the parent/carer's mood, relationships, leisure activities, and behaviour.

Response Predictors

- *Pain Stages of Change Questionnaire for Child (PSOCQ-A-13) and Parents (PSOCQ-P-13)* assess child's readiness to change and parents' own level of readiness to encourage their child to adopt a self-management approach.[95]Scores on the PSOCQ-A predict magnitude of response to an intensive PPRP e.g., strongest predictor of non-response to intensive pain rehabilitation treatment was lower readiness to change (Simons et al., 2017). The short form (currently being validated by Simons et al., 2024) uses 13 of the most useful items from the full questionnaire.
- *Chronic Pain Acceptance Questionnaire 2 item version (CPAQ-2)[96] and Parent (CPAQ-P)[97] 8 item version*.[98] Parent beliefs about child acceptance were negatively correlated with parent pain catastrophising and parent fear of pain; greater acceptance negatively associated with protective parent responses.[97] Changes in acceptance significantly predicted changes in depressive symptoms, catastrophising, and functional disability.[99] The 2-item version to be used in CYP includes the two items (9 and 14) from the full CPAQ that account for 60% of the variance.
- *Fear of Pain Questionnaire for Child Short Form (FOPQC-SF)[100] and Parent Version (FOPQ-P*[41]). The 8-item FOPQC-SF identifies pain-related fear and avoidance in youth during clinic evaluations, as this can levels of emotional distress and pain-related disability. It has moderate-to-strong construct and criterion validity, and preliminary evidence suggests responsivity to change.[100]

Global Satisfaction with Care

- to evaluate PPRP quality and associations with subsequent loss-to-follow-up (e.g. bias towards high or low satisfaction).
- patient and parent response to global question "How satisfied are you with your pain management" and answered on an 11-point numerical rating scale (NRS) with 0=very dissatisfied and 10=very satisfied" (as previously reported following intensive interdisciplinary pain management in CYP[101])
- global impression of change rated on 7-point Likert scale from very much improved to very much worse[88]
  - in addition, global impression of change will be rated by the PPRP clinical staff member assigned as the participant's Key Worker

- qualitative interview at end of PPRP and 3-month follow-up to seek views of participants and parents and document any negative effects

Educational attendance
- school attendance (% full-time) reported by parent and/or school

5.3.3 Physical Function
- specialist physiotherapy assessment of range of movement
- strength (Manual Muscle Testing-8 and MMT-3) of different muscle groups scored on 0-10 Kendall scale[102]
- 6-minute walk test[103]
- Childhood Myositis Assessment Scale (CMAS) assesses 14 proximal and distal muscle group functional tasks (score: 0-51).[104,105]

5.3.4 Health utilisation and costs
- *Child and Adolescent Service Use Schedule (CA-SUS)*[106] for collecting health and social care resource use has been modified for this study population, and includes:
  - healthcare utilisation
  - prescription and over-the-counter medications
  - selected items derived from institute for Medical Technology Valuation of Informal Care Questionnaire (iVICQ)[107] are incorporated in this study-specific version to reflect loss of paid work and additional unpaid time for caring activities related to their child's pain, and travel costs related to taking child to medical appointments/hospital visits
  - inter-current participant health conditions that influence health or economic outcome that are not directly attributable to pain and/or new health problems requiring use of health care or medication will be documented separately
- *Child Health Utility instrument 9 Dimensions (CHU-9D)*[108-110] for calculating quality adjusted life years within a trial

5.4 SCHEDULE of ASSESSMENTS (see also APPENDIX 2)

i) Usual Care

Following screening at Chronic Pain Clinic, and baseline assessment with PPRP clinical staff, eligible participants/families who consent to enter the study will be randomised.
Participants in the PPRP(Delayed) group will continue usual intermittent outpatient clinical care until entry into the PPRP intervention. CLINIC PROMs will be completed at each pain clinic appointment (approximately 3 monthly) as part of usual care:
- child-report: pain intensity, PedsQL-Child, PI-ED, PCS-Child
- parent-report: pain intensity, PedsQL-Parent, HADS, PCS-Parent

ii) Intervention phase
- 2 weeks prior to attending PPRP
  - Pre-habilitation pain education update (2 hr online/video session conducted by PPRP clinical staff)
- Day 1 of PPRP (first morning; immediate pre-intervention; research staff explain processes and complete or supervise data collection)
  - PPRP Case Report Form (current pain distribution; health care utilization including medication use; school attendance). Researcher completes with responses from participant and parent to directed questions.
  - completion of PPRP patient- and parent-reported outcome measures (PROMs). Research staff will provide participants and parents with instructions and training and support completion of questionnaires on REDCap.
  - physical function (physiotherapy assessment, 6-minute walk test).

- CA-SUS and CHU-9D questionnaires for health economic analysis completed by parent

- Day 19 of PPRP (final day of 3-week PPRP; immediate post-intervention; research staff explain processes and complete or supervise data collection)
  - completion of PPRP patient- and parent-reported outcome measures (PROMs).
  - physical function (physiotherapy assessment, 6-minute walk test)
  - acceptability of study design rated by participant/parent
  - satisfaction with PPRP and global impression of change rated by participant/parent; researcher asks for and documents negative effects or additional feedback

iii) Follow-up

- 1-month post PPRP
  - on-line check-in between member of PPRP clinical staff and participant
- 3-months post PPRP (attendance at Pain Centre; review by PPRP clinical staff and research staff collect outcome data and support completion of questionnaires on REDCap)
  - PPRP Case Report Form
  - completion of PPRP patient- and parent-reported outcome measures (PROMs)
  - physical function assessment
  - satisfaction with PPRP and global impression of change rated by participant/parent; researcher asks for and documents negative effects or additional feedback
- 6-months post PPRP (online; research staff schedule assessment with participant and parent/carer to collect outcome data)
  - PPRP Case Report Form
  - completion of PPRP patient- and parent-reported outcome measures (PROMs)
  - CA-SUS and CHU-9D questionnaires for health economic analysis
  - participant/parent satisfaction

5.5 DATA COLLECTION

All data will be handled in accordance with the UK Data Protection Act 2018, principles of GCP, and Priment CTU Standard Operating Procedures with trial specific arrangements detailed in a data management plan. Data will be collected at the following points:

- baseline information by PPRP clinical staff to confirm eligibility, and research staff will obtain consent/assent and then access the medical record for baseline/screening data);
- onsite physical function assessment and completion of PROMs Day 1 and Day 19 of PPRP
- follow-up PROMs at 3 months (on-site) and 6 months (online/telephone with participant and parent) (*see Appendix 2 Schedule of Assessments and Procedures*).

All participants will be assigned an anonymous participant identification code (Study ID number). (*see also Section 8.6 Data Protection and Patient Confidentiality).*

Study Documents

All Study Documents (eg.CRFs, record of participant/parent attendance and PPRP session delivery, adverse events) will be completed by research staff and labelled with Study ID only. Feedback and comments from participants/parents regarding satisfaction at the end of the intervention (Day 19 PPRP) will be transcribed by the researcher, labelled with Study ID, and securely stored.

Research Electronic Data Capture (REDCap) Database

REDCap is a GCP compliant cloud-based database used by GOSH and UCL which is stored within the Digital Research Environment at GOSH. The database will be built by the Priment CTU Data Manager, and tested by members of the trial team through User Acceptance Testing, before going live. Trial data variable names will be standardised so data can be easily analysed, and anonymised data can be shared between members of the GOSH research team and Priment CTU

staff. The trial data will be coded at the data entry stage using predefined structures and data entry rules. Back-ups of the REDCap trial database will be made on a monthly basis.

Databases provided by REDCap have the ability to provide electronic consent (eConsent) and electronic patient/parent reported outcomes (ePROMs). Screening data from the initial pain clinic appointment will be retrieved form the medical record using a standardised case report form (CRF) and entered into the RedCAP database by the GOSH research team. CRF data at baseline and follow-up will be verifiable from source data at site (i.e. EPIC electronic hospital record and securely stored hard copies).

PROMs will be directly completed in REDCap by participants and parents with a specific login, and the necessary processes will be explained and supervised by a member of the research team at face-to-face assessments (Day 1 PPRP, Day 19 PPRP, 3-month follow-up). Paper copies of all questionnaires are also available if participants or parents have difficulty with completing measures on a tablet or computer.

Prior to being granted access to REDCap, potential users will have completed Information Governance training within the last 12 months, and training will be provided by the Senior Data Manager or Priment Trial Manager. Research staff who are entering data into REDCap, and supporting participants/carer(s) with completion of PROMs questionnaires, will be listed on the PIIPeR site staff delegation log, and authorised by the PI to perform these duties. Each authorised staff member will be issued with their own unique login details for the RedCAP database, and a list of current users will be maintained in the Site File and by Priment. Staff will be instructed not to share their login details with other staff, and the RedCAP audit trail will record all entries/changes made by each user.

Data entered into REDCap will be subject to some basic validation checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning. Where necessary, corrections to data on the CRF can be made by site staff and entered into RedCAP. The RedCAP audit trail will record the original data, the change made, the user making the change and the date and time. To avoid the need for unnecessary data queries, fields will not be left blank on RedCAP, but will be recorded “Not Done”, Not Applicable”, “Not Available” or “Not Known” if every effort has been made to obtain the data. The relevant CRF forms and RedCAP entries will be completed as soon as possible after a patient’s visit.

At the completion of the feasibility trial, the REDCap database will be closed to Priment CTU, and transferred and maintained in the Digital Research Environment at GOSH, and the GOSH DRIVE (Data Research, Innovation and Virtual Environments) Team will support ongoing data collection for later stages of the programme grant. Data will be stored securely for twenty-five years.

5.6 STATISTICAL CONSIDERATIONS

Primary outcomes

- recruitment rate: proportion of CYP referred to GOSH Pain Service who fulfil eligibility criteria consenting to enter the study
- treatment time initiation rate: proportion of enrolled participants for who it was feasible to enter PPRP within the designated time-frame (1-3 months from randomisation for PPRP(early), 6-9 months for PPRP(delayed))
- treatment completion rate: proportion of enrolled participants completing the 3-week PPRP
- follow-up rate: proportion of enrolled participants who completed the 3 months and 6 months post-PPRP assessments

Secondary Outcomes

- intervention
  - proportion of sessions attended by parent/carer in 3-week PPRP ('dose received')
  - proportion of patient and parent programme sessions delivered according to timetable and manuals for planned interventions ('dose delivered'),

- acceptability of study design (0-10 NRS)
  - by participant, parent/carer, Pain clinic care team, PPRP staff
- participant and parent-reported satisfaction (0-10 NRS)
- global impression of change (7-point Likert scale)
  - by participant, parent/carer, PPRP Key worker
- adverse events and negative effects
  - type, severity, impact on PPRP attendance

- data collection
  - proportion of complete datasets: Case Report Form, PROMs and questionnaires, and physical assessments
    - each timepoint: Day 1 and Day 19 of PPRP; 3 months and 6 months post-PPRP
  - feasibility of health economic analysis
    - calculation of health and social care resource use with study-specific Child and Adolescent Service Use Schedule (CA-SUS)
    - calculation of quality adjusted life years with Child Health Utility instrument 9 Dimensions (CHU-9D)

Exploratory outcomes

- group differences in PedsQL-Child total score between the 2 randomised arms at 6-9 months post recruitment
  - 'active arm': 6-month follow-up after PPRP(Early)
  - 'control arm': follow-up after usual care prior to entry into PPRP(Delayed)
- longitudinal within-patient pre-post intervention change in PROMs (*primary measure:* PedsQL-Child and PedsQL-Parent total scores) in both arms
  - time points: Day 1 PPRP; final Day 19 PPRP; 3- and 6-month follow-up

Statistical Analysis Plan

Summary Of Baseline Data And Flow Of Participants

Data related to numbers assessed, randomised, allocated to intervention, lost to follow-up and analysed will be maintained in a Screening and Recruitment Log to construct a consort flow diagram (http://www.consort-statement.org/). Baseline participant characteristics (demographics, pain classification and duration) will be reported descriptively.

Primary Outcome Analysis

For each of the primary outcomes we will report the numerator, denominator, proportion and 95% confidence interval (95%CI). Confidence intervals will be based on an exact binomial distribution. For the treatment initiation, treatment completion, and assessment completion, we will report overall and by randomised arm.

Additional Outcomes Analysis

Analyses will be descriptive. We will report:

- the frequency and proportion of missing data for each of the study measures
- descriptive statistics (mean, SD, median, IQR or frequency and percentage, as appropriate) for all the study measures, at the different assessments
- frequency and type of adverse events.

We will report the mean and standard deviation of study design acceptability, for each of the participants, parents/carers, usual clinical care team, and PPRP team. This will be reported overall and by trial arm.

Exploratory analyses

For group differences between the two arms (early or delayed), we will compare PedsQL-Child Core total score

- 6 months post PPRP(Early) *versus* usual care prior to PPRP(Delayed)
- 6-9 months post recruitment in both groups

For the two arms (early or delayed) combined, we will also report:

- The attendance at the PPRP sessions, and the fidelity of delivering the PPRP intervention according to the protocol.
- The mean change (and 95% confidence interval) in PedsQL-Child Core total score between pre-intervention (Day 1 PPRP) and post-intervention (3-month and 6-month follow-up).
- The proportion (and exact confidence interval) of participants who achieved a PedsQL total score above 66 at 3 and 6-months post intervention.

Health Economic Analysis

The economic evaluation aims to assess the feasibility of collecting healthcare resource use and health related quality of life (HRQoL) data to inform the cost effectiveness analysis of the ongoing PIIPeR trial.

Healthcare resource use related to the intervention and pain management will be obtained from patient medical records. Other health and social care resource use, out of pocket costs, time off school and other wider support will be captured using the child and adolescent service use schedule (CA-SUS)[111] modified for the study population. The carer's paid and unpaid time for caring activities will be informed by items in the iVICQ [107], and incorporated in the study-specific CA-SUS.

Resource use will be costed using nationally published sources such as Personal Social services research unit (PSSRU)[112] and National Health Service (NHS) reference costs[113] Time-off work for caring and attending hospital appointments will be costed based on the human capital approach. Hourly wages will be obtained from the Office of National statistics based on self-reported occupational classification. We will calculate the cost of the intervention including staff employment, training, supervision, and time taken to deliver the intervention.

The CHU9D (child health utility 9D)[110] will be used to calculate the quality adjusted life years (QALYs) using the area under the curve method. We will report descriptive statistics including frequency, mean, standard deviation and proportion of missing data for costs and QALYs for each follow-up time point.

6 STUDY SETTING

Study Site

This single site study will be conducted at Great Ormond Street Hospital (GOSH). The Chronic Pain Clinic at Great Ormond Street Hospital (GOSH) is one of the largest UK paediatric pain clinics and one of few nationally commissioned services. The majority of referrals are received from London, the South East and East of England.[6] The PPRP will be integrated into the clinical care pathway for CYP managed by the Chronic Pain Service.

Over 240 CYP with chronic pain and varying degrees of pain-related disability are currently referred to the GOSH Chronic Pain Clinic each year, and this number is increasing. In relation to PPRP eligibility criteria (*see Section 7.1*) recent data for adolescents at referral to our chronic pain clinic (n=161, 70% female) aged 14.4±2.0 years (range 10-18 years) [58,114] identified:

- average pain intensity in the last week (0-10cm visual analogue scale) 6.3±2.0; moderate-severe range >4/10 in 93%
- PedsQL total score 48±19 (mean±SD, range 5-93); <70 (i.e. severe impairment) in 87%
- increased emotional distress: PI-ED score 16.5±6.6; >20 in 30%

- high pain catastrophising scores: PCS-C 29.0±11.5; >20 in 72%

Staff and Facilities

The PIIPeR Programme Grant funding has funded recruitment at GOSH of an interdisciplinary team (physiotherapists, psychologists, occupational therapists, advanced nurse practitioner), research staff (postdoctoral research associate and research nurse), support staff (project manager and medical secretary) and an initial 2-year collaboration with Priment Clinical Trials Unit.

The PPRP intervention will be delivered within the Mroue-Fateh Centre for Pain Management on Hummingbird Ward (www.gosh.nhs.uk/wards-and-departments/ward-and-admissions-information/hummingbird-unit/). This space has been renovated and configured exclusively for delivery of the PPRP. Facilities include: a large room for group discussions and activities for participants and/or parents with members of the interdisciplinary team, and for exercises led by physiotherapists; consultation and interview rooms for individual or small group interventions; a kitchen for family refreshments and activities such as baking led by occupational therapists; lounges for families; and office space for staff. Off-site hospital or local hotel accommodation will be provided for the participant and one parent/carer for families who need to travel for the intervention.

Research staff will be available on site to complete CRFs and explain outcome measures to participants and their parent/carer, and methods for accessing and completing questionnaires on REDCap. Follow-up data will be collected on site at 3 months when participants/family attend Hummingbird for follow-up and online at 6 months post PPRP. The research protocol does not include any additional hospital visits that are not part of usual care.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Participants will be children and young people (CYP) referred to the Great Ormond Street Hospital Chronic Pain Clinic. Following interdisciplinary assessment and completion of the PROMs collected at clinic as part of usual clinical care, potential participants eligible for PPRP will be identified by the clinical care team, and discussed with PPRP clinical staff.

7.1.1 Inclusion criteria

Inclusion Criteria

- CYP aged 11-18 years with chronic pain (>3 months duration) following referral to, and multidisciplinary assessment at, the GOSH Chronic Pain Clinic. Eligibility will not be influenced by biological sex, gender, ethnicity, or socioeconomic grouping.
- Willing and able to provide written informed Participant consent/assent and Parental consent
- Fulfil at least **3 of the 4** criteria:
  - significant pain-related disability (PedsQL quality of life total score <70)
  - high levels of pain catastrophising (Pain Catastrophizing Scale score >20)
  - school attendance <90%
  - psychological (Paediatric Index of Emotional Distress score >20) and/or physical (specialist physiotherapy assessment of reduction in mobility and muscle strength) comorbidity

Exclusion criteria

- Unwilling / unable to provide written informed Participant consent/assent and/or Parental consent
- Non-engagement and/or not willing to accept biopsychosocial formulation and management plan
- Major psychological or psychiatric illness (personality disorder, severe depression, eating disorder) that requires specific therapy
- Other acute intercurrent illness/infection that precludes involvement in group activities or ability to attend full-time Participant Timetable
- Parent/carer unable to attend for joint and parallel Parent Timetable
- Severe limitation of mobility due to intercurrent medical condition that precludes involvement in group activities (based on clinical history and medical and physiotherapy assessment)
- Any primary psychological disorder likely to interfere with engagement with the intervention including, but not limited to: externalising conduct disorder, chronic fatigue syndrome, functional neurological disorder, eating disorders (based on clinical psychology assessment at Chronic Pain Clinic and by PPRP clinical staff).
- Significant limitations in understanding of written and verbal English that would preclude the participants engagement in group activities and verbal discussions. As patients referred to GOSH Pain Clinic are usually attending UK schools, this exclusion would be rare. Parental language barriers are relative exclusion criteria. In line with current clinical practice, information for parents and consent can be obtained with interpreters, and some educational material can be translated from English. The extent to which parental understanding of verbal English would limit engagement in parent sessions and skills training would be assessed on an individual basis.

7.2 Sampling

Size of sample

Forty-eight participants will be recruited and randomised to PPRP within 12 months. Based on our pain service annual activity reports, audits and previous research studies enrolling GOSH Chronic Pain Clinic patients [58,114], we estimate that at least 80-100/year will fulfil eligibility criteria for PPRP, and 48 participants per year will be achieved even with a conservative enrolment rate of 60-70%.

Each PPRP lasts for 3 weeks and will include 4-6 participants. Ten programmes per year will be scheduled, with intervals between for PPRP clinical staff to perform prehabilitation education, baseline evaluations and 3-month clinical follow-up.

The second year of the feasibility phase will facilitate collection of 3- and 6-month post-intervention outcome data in all PPRP(Early) participants, and usual care data in all PPRP(Delayed) participants. A smaller proportion of PPRP(Delayed) participants will have completed 6-month post-intervention follow-up. All longitudinal post-intervention data collected within the time-frame of the feasibility period will be assessed. Longer-term follow-up will be conducted as part of further submissions to continue recruitment throughout the 10-year PIIPeR programme grant, with a protocol informed by the feasibility trial.

Sampling technique

A convenience sample of 48 consecutive participants recruited to PPRP will be included.
Participants in the following categories will be identified:

- Total referrals to Pain Clinic
  - Fulfil clinical inclusion criteria for PPRP

- Clinical criteria for exclusion (absolute/relative) and continue usual care

- PPRP Groups
  - fulfil clinical criteria for inclusion and provide consent/assent
    i. enter PPRP within the allocated timeframe for PPRP(Early) or PPRP(Delayed)
    ii. complete the intervention
    iii. withdraw from the intervention and/or follow-up
  - fulfil clinical criteria but decline research study recruitment/randomisation
    i. non-engagement with biopsychosocial model of care
    ii. family/social or other reasons

7.3 Recruitment

7.3.1 Sample identification

Participant Screening

Potential participants will be identified following referral and assessment at GOSH Pain Clinic, as per current practice. Information for referrers, is included on the GOSH Pain Service website. Participants will not be recruited through Patient Identification Centres (PICs), or by publicity (posters, leaflets, adverts or websites).

The results from multidisciplinary assessments and PROMs completed as part of usual clinical care will be used by the Pain Clinic care team to identify potential eligible participants for PPRP:

- multidisciplinary team (MDT) assessment at pain clinic encompasses
  - demographic data entered in electronic medical record (EPIC): age, sex, self-reported gender (if becomes available for self-report in EPIC for 16 years and over), ethnicity
  - medical diagnosis, history and examination, previous investigations and consultations
  - current and previous treatment (medication, psychological or physiotherapy interventions)
  - clinical psychology assessment
  - physiotherapy assessment and examination
  - school attendance
  - participant- and parent-reported outcome measures (PROMs) collected as part of usual clinical care and entered onto EPIC are reviewed
  - MDT biopsychosocial formulation and management plan

As part of current usual care, all new patients reviewed at Chronic Pain Clinic are presented and discussed at the weekly Pain Service MDT meeting (secure online meeting with all Pain Service staff). This will be attended by PPRP clinical staff and eligible participants for PPRP will be discussed.

A baseline assessment with PPRP clinical staff will be scheduled and Participant and Parent/Carer Information Sheets will be forwarded to eligible participants and families.

Baseline Assessment and Recruitment

Baseline assessment by PPRP staff will occur within 21 days of the clinical MDT weekly meeting. A secure online/video appointment will be conducted via the hospital network and electronic record (EPIC). PPRP staff will:

- review PROMs collected at pain clinic and clarify any further details regarding patient history to confirm eligibility

- answer additional questions from participant/family and discuss the intervention
- confirm receipt of Parent and Participant Information Sheets at least 24 hours previously
- check participant/family willingness to proceed and discuss recruitment with research team

Research staff will discuss the study, answer additional questions and seek participant consent/assent and parental consent. Research staff will not have access TO patient records until consent/assent has been obtained.

Participant recruitment will only commence when the trial has been:

- Initiated by the Sponsor (GOSH Research Governance / R&D), and
- Issued with the 'Open to Recruitment' letter or Green Light letter from the Sponsor.
- Registered on the ISRCTN Registry (https://www.isrctn.com/; studies designed to assess the efficacy of health interventions in a human population).

7.3.2 Consent

Parent Information Sheets and age-appropriate Participant Information Sheets (11-15 years, or 16-18 years) have been prepared in accordance with MCRN and HRA guidance. They are also informed by: previous PISs used in our adolescent population; Patient and Public Involvement activities by our Paediatric Pain Service PPI Lead; and guidance from the GOSH Young People's Advisory Group. The date when the Parent and Participant information sheets were received will be recorded in the medical case notes.

The Investigator, or a person delegated by the Investigator, will discuss the trial with potential participants and parent(s) or carer with parental responsibility to:

a) ensure adequate explanation of the aims, methods, anticipated benefits and potential hazards;
b) clarify trial procedures;
c) answer questions related to the trial.

Parental consent and participant consent (16 years and above) or assent (11-15 years) will be sought. Signed forms indicating participant consent/assent and parental consent will constitute enrolment.

The person taking consent will be GCP trained, suitably qualified and experienced, and will have been delegated this duty by the Investigator on the Delegation Log. Capacity of participant consent will be assessed according to NHS Health Research Authority guidance and documented in trial documents. Participants who have initially completed assent forms (11-15 years age), but reach 16 years of age during the period of the trial will receive a 16-18years PIS and be asked to complete a Consent Form.

The Investigator or designee will explain that participants are under no obligation to enter the trial, and this will not affect their usual clinical care at GOSH Chronic Pain Clinic. No clinical trial procedures will be conducted prior to the parent giving consent and the participant giving consent/assent by signing the consent forms. A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical/case notes/source documents.

Parents or participants can withdraw consent at any time during the trial, without having to give a reason, but if a reason is given this will be recorded in the case notes. Data already collected will be retained to protect the validity of the research, permissible as an exemption to data subject rights under GDPR. The participant will return to usual Pain Clinic care.

<u>Randomisation procedures</u>

All participants will be allocated a Study ID. Randomisation will be the last procedure to be completed at the Baseline visit. Priment CTU Standard Operating Procedure (SOP) for randomisation will be followed, with block-randomisation for allocation to PPRP (Early) or PPRP (Delayed) in a 1:1 ratio.

It is not possible to blind participants or PPRP clinical staff to the timing of the intervention. PPRP staff and families will be notified by research staff of the allocation to PPRP (Early) or PPRP (Delayed) at the end of the baseline visit to facilitate appropriate scheduling.

7.4 End of PIIPeR-Feasibility Study and subsequent PIIPeR-Trial follow-up

The 2-year feasibility study includes: recruitment for 12 months, randomisation to PPRP(Early) or PPRP(Delayed), and follow-up at 3 and 6 months. Data collected up to 21 months will be analysed in collaboration with the Priment CTU statistician, and the feasibility study will end at 24 months.

The PIIPeR Programme Grant provides funding to continue follow-up and recruitment. The design of the subsequent PIIPeR Trial will be informed by the feasibility phase (i.e. feasibility and acceptability of recruitment and randomisation).

Recruitment and randomisation will be closely monitored by the Trial Management Group, and presented to the Steering Committee at 6 months. A protocol for the ongoing PIIPeR Trial will be developed in collaboration with the Steering Committee and External Advisory Board, and submitted for ethical, regulatory and local research governance approvals. We aim to have these approvals in place to facilitate ongoing recruitment to PPRP, and long-term follow-up in patients recruited during the feasibility phase. Participants and families recruited during the feasibility phase will receive updated Participant Information Sheets and study documents, and be asked to consent to ongoing follow-up.

Early Stopping Criteria: If the feasibility or acceptability of the randomised design results in failure to fill available PPRP places, the trial may be stopped early. This will be based on the recommendation of the sponsor and CI or Trial Steering Committee. An alternate design (e.g. pre-post intervention longitudinal cohort) will be developed with input from the Trial Steering Committee and External Advisory Group. A new proposal and study documents for the ongoing PIIPeR Trial will be submitted for ethical, regulatory and local research governance approvals. This will include updated recruitment criteria, and will also include longer term follow-up both for new patients and for participants enrolled in the PIIPeR-Feasibility phase.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

All participants will be managed by an interdisciplinary team of healthcare specialists (PPRP Clinical Team). This intervention will be part of the clinical care pathway for patients referred to the Chronic Pain Service.

INTERVENTION/ ASSESSMENTS	POTENTIAL RISK	RISK MANAGEMENT
Paediatric Pain Rehabilitation Programme (PPRP)	Recruited patients not appropriate for intervention	MDT includes biopsychosocial assessment and formulation, and review by an experienced physician, clinical nurse specialist, psychologist and physiotherapist. These will be discussed with PPRP staff who will confirm eligibility on the basis of the clinical history, and then discuss the PPRP with potential patients and families. Subsequent questionnaires at the beginning and end of PPRP, will evaluate willingness/readiness to engage, and

		progress during PPRP will be documented. If enrolled patients are subsequently felt to not be appropriate for the intervention, criteria for recruitment will be discussed by PPRP staff and the clinical care team. PPRP staff will also share results with the TSC to review recruitment and identify any potential refinement of eligibility criteria.
	Physical/emotional effects related to programme intensity	Exclusion criteria include significant psychological/psychiatric and physical impairments that preclude active participation in the PPRP. The PPRP intervention team (psychologists, clinical nurse specialists, physiotherapists, occupational therapists) have clinical skills to identify and assess risk for participants and manage physical and emotional effects that arise during PPRP and: i) address these within individual sessions during the PPRP timetable; ii) adjust individualised plan as needed; or iii) withdraw the participant from the intervention if clinically indicated or according to participant/family preference.
	Separation from other family or peers during PPRP	Intervention delivery team will assess risk. Withdrawal from intervention if clinically indicated. Return to usual care pathway.
	Unmasking family tensions	Usual MDT care team will assess this at referral, and the PPRP team will continue to assess risk throughout the intervention. Withdrawal from intervention if clinically indicated. Return to usual care pathway.
	Family financial costs	Access to designated hospital accommodation or suitable local establishments for families requiring assistance. Access to travel costs for hospital attendance in accordance with GOSH and NHS guidance.
	Non-compliance	Patient and parent/carer attendance throughout the 3-week programme will be monitored and barriers to attendance identified.
Intervention Follow-up (within clinical care pathway)	Effort/sacrifices to change behaviours	PPRP staff will identify individuals with difficulties, identify contributing factors, and manage this with extra individual sessions if needed. Patients not achieving or maintaining sufficient gains at follow-up will be provided with additional support from PPRP staff and/or return to the usual clinical care pathways according to clinical need.
	Difficulty self-implementing strategies into ongoing daily lives	
	Questionnaire scores at level indicating clinical co-morbidity (e.g.	Research team/PI will discuss with clinical care team.

	anxiety, depression, pain catastrophising)	
Incomplete data during clinical care pathway	Data collection at initial assessment, pre and post PPRP, and clinical care follow-up incomplete	Regular review by research team to check data availability prior to and following completion of 3-week PPRP; check medical record and/or contact participants for missing data.
Incomplete data during trial follow-up	Loss to follow-up	Details in PIS regarding longitudinal follow-up and consent sought for regular follow-up via online and/or face-to-face completion of outcome data.
Data handling	Data breach; failure of confidentiality	All research and PPRP team members will maintain mandatory Information Governance and GCP training and this will be checked at Site Initiation. All regulatory requirements (Ethics, HRA, Local R&D) will be obtained prior to study onset. A Data Privacy Impact Assessment will be completed and the study will be registered with the sponsor's data protection department. Any data that is collected that contains Personal Identifiers such as name, address, NHS numbers will be included in a linking file that is securely stored in a locked cabinet inside a GOSH clinical area that can only be accessed with swipe card and key lock entry. All participants consenting to the study will be assigned a Study Number and only pseudonymised data will be entered into the study database. Data Protection Act, Sponsor and PRIMENT guidance on data sharing will be followed.

STUDY DESIGN	POTENTIAL RISK	RISK MANAGEMENT
Randomisation	Families decline randomisation to PPRP(Early) versus PPRP(Delayed)	Recruitment and randomisation will be closely monitored by the Trial Management Group, and presented to the Steering Committee at 6 months The trial may be stopped before completion on the recommendation of the sponsor and CI or Trial Steering Committee if difficulties with the feasibility or acceptability of the randomised design result in failure to fill all available PPRP places. An alternate design will be developed with input from the Trial Steering Committee, and an amended proposal submitted for regulatory approvals.
	Families and/or clinicians rate randomisation as unacceptable	
	It is not feasible to enter PPRP within the proposed time frames (Early 1-3 months and	Any significant participant or family factor (e.g. major exams, or family illness) that precludes entry within this designated timeframe will be discussed on a case-by-case basis, and the reason will be documented in the medical records and the CRF. The

	Delayed 6-9 months post-recruitment)	family will be offered dates across a wider timeframe but as close as feasible to the randomised time window. This will ensure that eligible participants who have already provided consent/assent are not denied access to the intervention.
Recruitment	Inadequate recruitment results in unfilled places in the PPRP.	To ensure all available places in the PPRP are accessible, an option to rescreen GOSH Chronic Pain Clinic patients at later points in the clinical care pathway will be discussed with the Trial Steering Committee and Sponsor. In addition to fulfilling stated Inclusion Criteria for PPRP, participants eligible for re-screening may fulfil one of the following: • initial decline of PPRP due to inability of parent/carer to attend that has now resolved • resolution of acute intercurrent illness/infection that precluded involvement in group activities or ability to attend full-time Participant Timetable • increasing pain-related disability that now fulfils criteria for inclusion • previously unwilling or unable, but now willing and able, to provide written informed Participant consent/assent and Parental consent. The time point from referral to entry into PPRP, and the reason for re-screening will be documented in the source documents.

Discontinuation / Withdrawal From PPRP

Discontinuation for Clinical Reasons
A participant may be withdrawn from the intervention if the PPRP clinical care team decide continued participation is no longer in the participant's best interests. Reasons for withdrawal will be recorded. Reasons for discontinuing treatment may include:

- inability or failure of participant and/or parent to engage in, and attend, the interdisciplinary intervention
- persistent non-compliance to protocol requirements
- adverse events that prevent engagement in PPRP sessions
- intercurrent illness which prevents further attendance
- any alterations in the participant's condition which justifies the discontinuation of treatment, as determined by the clinical care team

The decision to withdraw a participant from the PPRP intervention will be recorded in the CRF and medical record. The importance of ongoing collection of PROMs after PPRP discontinuation as part of usual clinical care will be highlighted.

Participant withdrawal from PPRP or follow-up
If a participant wishes to withdraw from the PPRP, despite discussions and support from the PPRP clinical team, this decision, dates of attendance, and proportion of programme completed will be recorded in the CRF and medical case notes. The participant and parent/carer may withhold their reason for withdrawal, however, if a reason is given this will be recorded. Data already gathered at the point of withdrawal will be retained, as a permissible exemption to data subject rights under GDPR, in order to protect the validity of the research.

Patients who do not complete the program will return to usual clinical care pathways in GOSH Pain Clinic. Consent/assent will be sought for follow-up data from PROMs completed at pain clinic to be

entered into the database to facilitate analysis and comparison of all available baseline and follow-up data.

If a participant withdraws from follow-up data-collection, the date and any reason (if given) will be recorded in the research database. Data up to the date of withdrawal will still be retained to protect the validity of the research, permissible as an exemption to data subject rights under GDPR.

Negative Effects

Expected negative effects of the intervention that will be managed by the PPRP clinical team, and not be classified as adverse events but will be documented in the Negative Effects Log include:

- increased participant anxiety or emotional discomfort during group or individual psychology or education sessions
- increased parental anxiety or emotional discomfort during group or individual psychology or education sessions
- initial increased anxiety as participants and/or parents navigate switch to self-management techniques and potentially reduce reliance on medication
- initial increased pain or new-onset musculoskeletal pain as a result of increasing graded physiotherapy exercises
- altered sleep pattern due to changing physical activity or challenging thoughts during psychology sessions

Adverse Events

Information related to any adverse events that prevent completion of PPRP and/or require further medical intervention/assessment/evaluation will be collected by staff delivering the intervention and conducting clinical follow-up, or by the PI or designee in the research team. Adverse events will be documented in the participant medical notes, and reviewed and managed by the clinical care team.

A record of adverse events labelled with the participant Study ID but no identifiable personal data will be securely stored by research staff, and include details of the type of event, management by clinical staff, and related impact on PPRP attendance. AE data transferred to Priment CTU will also be identified by the participant Study ID only to maintain confidentiality.

Adverse Events that meet the definition of a Serious Adverse Event will be recorded on an SAE Report Form by the CI or designated individual and the Sponsor will be informed. The Chief Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Safeguarding

All participants will be managed by an interdisciplinary team of healthcare specialists (PPRP Clinical Team) who are part of the GSH Chronic Pain Service. All clinical and research staff will maintain mandatory training requirements in relation to the NHS Core Skills Training Framework: Safeguarding Children Level 3; Safeguarding Adults; Preventing Radicalisation - Prevent Awareness and Prevent. Any safeguarding concerns will be discussed or reported via established processes at Great Ormond Street Hospital, which has a Safeguarding Service, Named Nurse and Named Doctor for Safeguarding, with 24-hour contact details on the hospital website. The Pain Service also has an assigned social worker who attends the weekly multidisciplinary meeting and is available for advice regarding less urgent issues.

8.2 Research Ethics Committee (REC) and other Regulatory Review & Reports

Regulatory Review & Compliance

The Chief Investigator or designee will ensure that the trial protocol, participant and parent information sheets, consent/assent forms and all supporting documents have been submitted for review and

approval. For this single site study, local regulatory approvals will be gained from the Great Ormond Street Hospital (GOSH) Research Governance team, and the Sponsor will ensure that the protocol, all supporting documents and IRAS application have been approved by the HRA and an appropriate research ethics committee.

Before participants are enrolled into the trial, the Chief Investigator or designee for this single site study will apply for local confirmation of capacity and capability.

The CI will submit a Final Report within 12 months of the completion of the study (https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/final-report-form/). If the trial is terminated prematurely, a final report will be made within 30 days after the end of the trial.

Amendments

This is a single site study involving the NHS. The Chief Investigator will discuss any potential amendments with the Trials Steering Committee. For any agreed amendment, the Chief Investigator or designee will submit relevant information and confirm arrangements to implement the amendment to the Sponsor. The GOSH Research Governance team will decide if the amendment is substantial or non-substantial for the purposes of submission to the REC. The updated protocol will be labelled with the next sequential number, date of the amendment, and details will be included in Appendix 3. Any amended study documents will also labelled with the next sequential number and date of the amendment. A valid notice of amendment will then be submitted to the REC for consideration, and to the Health Research Authority.

8.3 Peer review

The PIIPeR Trial Programme Grant was submitted in response to a Commissioned Call from Great Ormond Street Hospital Charity.
Initial review was conducted by the GOSHC Research Assessment Panel, which is made up of external scientific members from across the UK. The role of the panel is to:

- Assess research project and programme funding.
- Make recommendations to the Grants & Impact Committee for projects with high scientific merit, with a clear potential for patient benefit and that fit into the relevant scheme's remit and the wider charity research strategy.
- Evaluate progress of charity funded projects against defined goals.

An initial feasibility trial with a randomised design was recommended, with input from a Clinical Trials Unit. We responded to feedback from the RAP and incorporated their suggestions in a subsequent submission.

The revised PIIPeR Programme Grant (which incorporated both the initial feasibility study and ongoing plans) was sent for external peer review by GOSHC. High quality peer review included 5 independent external reviewers, with expertise in paediatrics and/or pain management who considered the clinical and/or service based aspects of the protocol, and/or had the expertise to assess the methodological aspects of the study. Reviewer comments were sought under the following headings: importance; scientific quality; feasibility and quality of research design; potential benefit and impact for children; ethics; data management; and resources requested.

Our responses to the Reviewer Comments were submitted to GOSHC. The project and our responses were presented and discussed at an External Advisory Group meeting, chaired by an independent external academic, and attended by a statistician, 2 clinical academics with expertise in paediatric pain management, and representatives of GOSH Charity Grants. The application was subsequently approved, and the first 3 years of the programme grant funding were released.

8.4 Patient & Public Involvement

Design of research

- Patients with chronic pain managed by the Pain Service at GOSH, and the GOSH Young Peoples Advisory Group (https://www.gosh.nhs.uk/our-research/our-research-infrastructure/nihr-great-ormond-street-hospital-brc/patient-and-public-inv/ppi-researchers/) have contributed to patient and public involvement and engagement (PPIE) activities related to chronic pain research in CYP. This has been led by Dr Helen Laycock, a Pain Consultant and member of the clinical team who has formal training in PPIE.
- Participant and Parent Information Sheets have been prepared in accordance with MCRN and HRA guidance. They are also informed by: previous PISs used in our adolescent chronic pain population; activities by our PPIE Lead; and guidance from the GOSH Young People's Advisory Group.
- Chosen assessment tools encompass mandatory, important, and research domains within the core outcome set for paediatric chronic pain trials and longitudinal clinical care. This was developed with input from health care providers, adolescents with pain, and parents.[76]
- Patient and public representatives were included as co-authors and identified the goals outlined in the Lancet Adolescent and Child Health Commission "Delivering transformative action in paediatric pain".[115] Our proposal is relevant to all four goals: 'make pain matter' by raising awareness amongst healthcare providers and research funders to consider and prioritise pain in children; 'make pain visible' by using outcome measures across multiple domains of physical and psychosocial function; 'make pain understood' by investigating trajectories of pain and pain-related disability and response to different aspects of treatment; and 'make pain better' by providing access to a family-focussed intervention for children with chronic pain.

<u>Acceptability of intervention</u>

- The current programme grant and funding is based on a family's lived experience of chronic pain in childhood and the benefit achieved from a PPRP intervention at an overseas centre.
- A preliminary PPRP has been conducted to develop and refine the timetable, sessions and activities. Five children aged 11-16 years who are currently being managed at GOSH Chronic Pain Clinic and their parent/carer attended each day and completed the 3-week PPRP intervention. All proposed study measures (including the battery of validated questionnaires for patients and parents, physical assessments, and final day satisfaction and feedback interview) were completed on the first and last day of the PPRP. Patients and parents appreciated having a researcher present to answer any questions, but also felt that the questionnaires were easy to understand, and assessments took an acceptable amount of time. The following feedback was obtained, with satisfaction rated on 0-10 numerical rating scale (0=not at all satisfied; 10 = completely satisfied):
    - <u>young person feedback (n=5)</u>
        - satisfaction with how programme has supported you to manage and live alongside your pain: 8, 10, 10, 5 = 8.25 (ave)
        - satisfaction with activities: 7.5, 10, 10, 8, 10 = 9.1 (ave)
        - all said they would recommend the programme to others
    - <u>parent feedback (n=5)</u>
        - satisfaction with how programme has helped your understanding of how to support YP with managing/living alongside their pain: 8, 10, 9, 8, 8 = 8.6 (ave)
        - satisfaction with how programme has supported YP to manage/live alongside their pain: 7, 9, 8, 9, 7 = 8 (ave)
        - satisfaction with activities: 9, 10, 8, 10, 7 = 8.8 (ave)
        - all would recommend the programme to others

<u>Management of Research and Dissemination</u>

- The PIIPeR postgraduate research associate (Dr Anna Fieldwalker) has further presentations and meetings planned with GOSH YPAG to discuss ongoing aspects of the trial, and gain

feedback and advice regarding data collection. Methods for effective dissemination of reports and anonymised results in formats of interest to young people will be planned.

- A patient/public representative will join the Trial Steering Committee and provide input relevant to patient experience, review progress with recruitment, patient/family satisfaction, and provide input/advice for further research protocols, and dissemination of results.

8.5 Protocol compliance

Participant and parent compliance

Participant and parent/carer attendance for all sessions during the PPRP will be documented ('dose received - exposure'). The proportion of enrolled CYP and parents completing the 3-week PPRP will be reported as a feasibility outcome. Participant and parental satisfaction with the intervention will be recorded on a numerical rating scale ('dose received - satisfaction'), and their specific comments/suggestions will be recorded (labelled with Study ID)

Compliance with PPRP programme

Compliance with standardised programme delivery and treatment fidelity will also be assessed:

- proportion of patient and parent programme delivered according to timetable and manuals for planned interventions (treatment fidelity)
- audio or video recordings of randomly selected sessions will be assessed by independent raters for performance according to protocol (number of essential elements delivered; 'dose delivered'), and protocol deviations[73]

Non-compliance

Deviations from the protocol, or accidental breaches of the protocol that do not affect the safety of the participants, data security and the scientific value of the study will be documented, and reported to the CI and Sponsor and Priment CTU.

A serious breach is defined as a breach of the protocol which is likely to significantly affect the safety or physical or mental integrity of the participants, or scientific value of the trial. Persistent non-compliance with the protocol or principles of GCP and failure to report SAEs/SARs may be deemed a serious breach. While the likelihood is low in this single site non-CTIMP, any serious breaches will be reported to the Sponsor and Priment CTU and the REC will be informed within 7 calendar days.

Monitoring

The CI or designee for this single site study will agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections and provide direct access to source data/documents as required.
Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. Priment or its representatives will conduct all monitoring in compliance with the participant consent, site policy and data protection requirements.

Priment CTU performs centralised monitoring, which requires the submission of documents for review, including but not limited to the: Delegation Log; Screening Log; and Recruitment Log (including recruitment Y/N, randomisation date, PPRP entry date). Priment CTU will determine the appropriate level and nature of monitoring required, based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Priment or its representatives will send emails to the site CI or designee requesting the documents when required. The CI will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency determined for the trial.

On-site monitoring visits may be scheduled following Priment CTU review and/or where there is evidence or suspicion of non-compliance at the site with important aspect(s) of the trial protocol/GCP requirements. The site will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote monitoring activities conducted at a location remote from the research site replicate some on-site activities e.g. source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to the participating site (e.g. global pandemic) or conducted routinely. Details of remote monitoring will be agreed with the study site, conducted in accordance with site policy, and documented in the monitoring plan. The Site will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing remote monitoring. Remote monitoring will be conducted by Priment or its representatives via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties.

Following on-site/remote monitoring, the Priment Trial Manager will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The CI will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

8.6 Data protection and patient confidentiality

The Chief Investigator will be the data custodian. All members of the research team will have received and maintain up-to-date data security, GDPR, and information governance training. Data will be handled in a way that ensures appropriate security, including protection against unlawful or unauthorised processing, access, loss, destruction or damage in compliance with the requirements of the Data Protection Act 2018.

All participants will be assigned an anonymous participant identification code (study number). An identification sheet (linking file) which includes the patient name and study number will be kept on site in a separate locked filing cabinet in a secure location that requires GOSH ID badge swipe access and/or stored electronically on GOSH on-site password-protected computers with a link to the document folder only provided to PPRP clinical and research staff. Patient data will be retrieved from EPIC, the electronic patient system where relevant data are gathered and stored as part of usual patient care. This data will be extracted and added to a cloud-based REDCap database, overseen by the Priment Data Manager in collaboration with the Digital Research Environment (DRE) team at GOSH. Participants and parents will also have individual login details for completion of validated questionnaires on REDCap. At the end of the feasibility study the REDCap database will be transferred to the DRE team at GOSH. Ongoing follow-up and recruitment will continue following submission and regulatory approvals for later stages of the PIIPeR Trial.

Any hard copies of Case Report Forms awaiting upload into REDCap will be labelled with a Study ID only and kept in a locked filing cabinet (separate from the identification sheet). No identifying personal data will be entered into research databases. Any data transmitted to sponsors and co-investigators will be labelled only with the Study ID and will not contain identifying personal data. Access to data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

Electronic data being used for preparation of presentations and manuscripts will be stored in encrypted, password-protected computers within GOSH Data Research, Innovation and Environments (DRIVE) unit. We will comply with the requirements in the R&D Data Protection Registration Form.

At the end of the feasibility trial, the data belong to Great Ormond Street Hospital NHS Foundation Trust and the RedCAP data file will be maintained by GOSH. Following study completion, pseudonymised data and all essential documents will be archived and retained in compliance with the Data Retention Policy and principles of the Data Protection Act 2018. All archived documents will continue to be available for inspection by appropriate authorities upon request. Data will be stored for a minimum 25 years. Our Research Ethics submission will include seeking consent to combine results with future studies.

8.7 Indemnity

Great Ormond Street Hospital NHS Foundation Trust (trial sponsor) is covered by the NHS indemnity scheme and holds insurance against claims from participants for injury caused by their participation in the clinical trial. This includes insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the design or conduct of the research. As this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial.

Participants may be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of Great Ormond Street Hospital NHS Foundation Trust. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. Great Ormond Street Hospital will provide clinical negligence insurance cover for harm caused by their employees.

This is a single site study. There is no exposure of participants or staff to radiation (eg. X-rays, CT scans) and no procedural interventions or diagnostic tests are required. Risk assessments and protocols have been developed for activities that will be supervised by the clinical care team (eg. DO sessions: occupational therapy and baking, physiotherapy and physical activities, excursions to practice self-management).

Parent Information Sheets and Participant Information Sheets for 16-18 years olds will include details regarding processes for discussing concerns, reporting harm or seeking compensation, and availability of the National Health Service complaints mechanisms will be highlighted. Contact details for the Patient Advice and Liaison Service (PALS) at Great Ormond Street Hospital are included (Email: pals@gosh.nhs.uk Tel: 020 7829 7862).

8.8 Access to the final study dataset

The Chief Investigator, members of the PIIPeR research team at GOSH, and Priment CTU staff will have access to the full dataset. Group-level raw data will be presented within publications. Supply of anonymised research data to other investigators will be considered in accordance with GOSH governance and data sharing guidelines.

These data may be used for secondary analysis, and all PIS and consent forms will reflect this option. Parents are asked for consent for their child's anonymised data, and participants are asked to consent/assent for their anonymised data to be used in any secondary analysis or be included with future research studies.

9 DISSEMINATION POLICY

9.1 Dissemination policy

As the study sponsor, Great Ormond Street Hospital own the data arising from the study.

Progress and interim results will be shared with the clinical team, Steering Committees, and GOSHCC Advisory Group at regular intervals and on request. Results will be shared with other healthcare professionals and researchers via:

- Monthly research updates to GOSH Pain Service
- Presentations at national and international meetings
- Existing teaching and training programmes (Faculty of Pain Medicine & RCPCH; GOSH Paediatric Pain Network meetings and Annual Paediatric Pain Symposium)
- Public engagement activities, including ongoing presentations for GOSHCC and Donors
- Multidisciplinary networks that include family and patient groups
- Open-access peer-reviewed publications.

Study information can be discovered through study registration, open-access publications, and conference presentations.

Participating investigators will have rights to publish study data. There are no time limits or review requirements on these publications. The GOSH charity will be acknowledged within said publications but do not have publication rights.

Regarding participant notification of the study outcome(s), the PIS will include an agreement to providing contact details (e.g., email address) if they wish to receive newsletters about the study, as well as an option to receive a final summary report via newsletter or publication.

Regarding data availability, data supporting this study will be summarized in manuscript tables, and figures will represent individual data points. Additional data will be included in Supplemental Materials. Data will be available on reasonable request to the corresponding author, subject to approval by the investigative team. Regarding access to study protocol, full study report, anonymised participant level dataset and statistical code for generation of results will also be available upon reasonable request to the Chief Investigator.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Results and plans to submit manuscripts for publication will be discussed with the CI, site investigators, and Priment CTU staff.

Authorship of manuscripts submitted for publication will be in accordance with criteria defined by The International Committee of Medical Journal Editors criteria for authorship of manuscripts submitted for publication. Professional writers will not be used.

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11. APPENDICES

11.1 Appendix 1 – Required documentation:

Study documents

- PIIPeR Feasibility HRA Protocol V1.0 19_7_24
- PIS: 11-15yo, 16+yo, Parent; V0.2 12_7_24
- Consent Forms: 16+yo, Parent
- Assent Form: 11-15yo
- Withdrawal Forms: Parent, 16+yo
- Validated Questionnaires:
    - Pain VAS

  - PedsQL (Child/Teen Report & Parent Report)
  - Pain Catastrophising Scale (Child version & Parent version)
  - PI-ED
  - PROMIS Pain Interference
  - PROMIS Sleep Disturbance
  - Emotional Approach Coping-8
  - Hospital Anxiety & Depression Scale
  - Bath Adolescent Pain – Parental Impact Questionnaire (section 6)
  - Chronic Pain Acceptance Questionnaire (Adolescent short form; Parent version)
  - Fear of Pain Questionnaire (Child short form)
  - CHU-9D
- Non-validated Questionnaires:
  - Pain Stages of Change Questionnaire – Short Form (Parent version & Child version, currently undergoing validation process)
  - Fear of Pain Questionnaire (Parent short form, currently being validated)
  - CA-SUS (Parent-reported)
  - Satisfaction: Global Impressions of Change; Treatment Satisfaction Scale (NRS); interview: valued sessions, self-reported negative effects
  - Acceptability of Trial Design (i.e., Randomisation; NRS 0-10)
- CRF (Patient datasheet)
- Participant Logsheet (Linking File)
- Participant / Parent Attendance Log V0.1 18_7_24
- Programme Delivery Log V0.1 18_7_24
- Negative Effects Log V0.1 18_7_24
- Adverse Events Log V0.1 18_7_24
- Global Impression of Change_ PPRP Staff V0.1 19_7_24

<u>Supporting Documents</u>

- Cover Letter
- CVs
- PIIPeR Programme Grant External Peer Reviewer Comments
- Award Letter from Great Ormond Street Charity: 3 years PIIPeR Programme Grant
- HRA Approval confirmation for PiCCoLO study (sub-study of PIIPeR programme grant)

AMENDMENT September 2024: UPDATED AND ADDED DOCUMENTS

- PPRP_PIS Parent_V0.3 10_09_24
- PPRP_PIS 11-15_V0.3 10_09_24
- PPRP_PIS 16-18_V0.3 12_09_24
- PPRP_Invitation_Letter V0.2_10_9_24
- PPRP_PIS Parent_School Info_V0.1_11_9_24
- Pain Management Programme Clinical Information Leaflet V0.2 10_09_24

11.2 Appendix 2 – Schedule of Assessments and Procedures

	SCREENING Chronic Pain Clinic	BASELINE PPRP ASSESSMENT	USUAL CARE	PREHAB EDUCATION	PPRP INTERVENTION (Early or Delayed)		FOLLOW-UP POST PPRP		
Time Course	Discuss at Pain MDT	Within 6 weeks of MDT		2 weeks pre-PPRP	Day 1 (3wk PPRP)	Final Day (3wk PPRP)	4 wks (±7dys)	3 mths (±21 dys)	6 mths (±28 dys)
Site	GOSH Outpatients	online	GOSH/ online		Pain Centre daily attendance		online check-in	Pain Centre	online
CLINICAL ASSESSMENTS									
Interdisciplinary Assessment/Management	X		X						
Pain History / Examination	X		X						
CLINIC PROMs(child/parent)	X		X						
RESEARCH ASSESSMENTS									
Eligibility confirmation		X							
Consent & Randomisation		X PPRP Early or PPRP Delayed							
Pre-PPRP Preparation				X					
PPRP Staff Assessment		X			X	X		X	
OUTCOMES									
Physical function					X	X		X	
PPRP PROMs (child / parent)					X	X		X	X
CA-SUS; CHU-9D					X				X
Acceptability of Trial Design					X			X	
Participant/Parent Satisfaction						X		X	

11.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	15_9_2024	S Walker	Addition of Section 7.4 End of study
2	3.0	20_10_2025	S Walker	1. Study Timeline (Appendix 2) Increase from 15 days to 6 weeks 2. Feasibility of PPRP Entry Dates (proportion unable to attend within Early (1-3 months) or Delayed (6-9 months) time frame due to significant participant/family issues 3. Consent Forms: Inclusion of anonymised data in future studies optional

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.

11.3 Appendix 4 PPRP TIMETABLE

Week 1	"On-boarding"						
	Monday (1)	**Tuesday (2)**	**Wednesday (3)**	**Thursday (4)**	**Friday (5)**	**Saturday (6)**	**Sunday (7)**
09:00	09:00 Welcome					Weekend activities * Weekend goals * Individualised HEP/activity plan	
09:15	09:15 - 13:15 Initial Assessments (Individual timetables) *Physical assessments *Goal Setting *Outcome collection	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in		
09:30							
09:45							
10:00		10:00 - 11:00 DISCOVER Session Making a start	10:00 - 11:00 DISCOVER Session Pacing	10:00 - 11:00 DISCOVER Session Thoughts & feelings	10:00 - 11:00 DO Session Kitchen session		
10:15							
10:30							
10:45							
11:00		Break (15 mins)	Break (15 mins)	Break (15 mins)	Break (15 mins)		
11:15		11:15 - 12:30 MOVE Session	11:15 - 12:30 MOVE Session	11:15 - 12:30 MOVE Session	11:15 - 12:15 MOVE Session		
11:30							
11:45							
12:00							
12:15					12:15 - 13:30 EXPLORE Session Review of the week and goals for the weekend		
12:30		12:30 - 13:15 Lunch (45 mins)	12:30 - 13:15 Lunch (45 mins)	12:30 - 13:15 Lunch (45 mins)			
12:45							
13:00							
13:15	13:15 - 14:00 Lunch (45 mins)	13:15 - 14:15 DISCOVER session Making a start #2	13:15 - 14:15 DISCOVER session Pacing #2	13:15 - 14:15 DISCOVER session Thoughts & feelings #2	Home at 13:30		
13:30							
13:45							
14:00	14:00 - 16:30 Group Welcome *Introduction to team *Ground rules *Introduction to PPMP *Pain Education	Break (15 mins)	Break (15 mins)	Break (15 mins)			
14:15							
14:30		14:30 - 15:45 DO Session Pain volume and comfort toolboxes	14:30 - 15:45 DO Session Pacing games	14:30 - 16:15 DO Session Relaxation circuits			
14:45							
15:00							
15:15							
15:30							
15:45		15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind				
16:00							
16:15				EXPLORE - Unwind			
16:30	16:30 End of day	16:30 End of day	16:30 End of day	16:30 End of day			

Week 2	"Consolidation"						
	Monday (8)	Tuesday (9)	Wednesday (10)	Thursday (11)	Friday (12)	Saturday (13)	Sunday (14)
09:00						Weekend activities * Weekend goals * Individualised HEP/activity plan	
09:15							
09:30	09:30 - 10:15 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in		
09:45							
10:00		10:00 - 11:00 DISCOVER Session Challenging unhelpful thoughts	10:00 - 11:00 DISCOVER Session Sleep Management	10:00 - 11:00 DISCOVER Session Acceptance	10:00 - 11:00 MOVE Session		
10:15	10:15 - 11:15 MOVE Session						
10:30							
10:45							
11:00		Break (15 mins)	Break (15 mins)	Break (15 mins)	Break (15 mins)		
11:15	Break (15 mins)	11:15 - 12:30 MOVE Session	11:15 - 12:30 MOVE Session	11:15 - 12:30 MOVE Session	11.15 - 12:15 DO Session Prepare shared lunch		
11:30	11:30 - 12:30 Key Worker Time						
11:45							
12:00							
12:15					12:15 - 13:30 EXPLORE Session Review of the week and goals for the weekend		
12:30	12:30 - 13:15 Lunch (45 mins)	12:30 - 13:15 Lunch (45 mins)	12:30 - 13:15 Lunch (45 mins)	12:30 - 13:15 Lunch (45 mins)			
12:45							
13:00							
13:15	13:15 - 14:15 DISCOVER session Communication	13:15 - 14:15 DISCOVER session Challenging unhelpful thoughts	13:15 - 14:15 DISCOVER session Daily routines	13:15 - 14:15 DISCOVER Session Acceptance #2	Home at 13:30		
13:30							
13:45							
14:00							
14:15	Break (15 mins)	Break (15 mins)	Break (15 mins)	Break (15 mins)			
14:30	14:30 - 15:45 DO Session Communication games	14:30 - 15:45 DO Session Going out for a drink	14:30 - 15:45 DO Session Meal prep and shopping planning	14:30 - 15:45 DO Session Going to the shops			
14:45							
15:00							
15:15							
15:30							
15:45	15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind			
16:00							
16:15							
16:30	16:30 End of day	16:30 End of day	16:30 End of day	16:30 End of day			

Week 3	"Self-management and generalisation"						
	Monday (15)	**Tuesday (16)**	**Wednesday (17)**	**Thursday (18)**	**Friday (19)**	**Saturday**	**Sunday**
09:00					09:00 - 13:00 Final Assessments (Individual timetables) *Physical assessments *Goal Setting *Outcome collection		
09:15							
09:30	09:30 - 10:15 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in	09:30 - 10:00 EXPLORE - check in			
09:45							
10:00		10:00 - 11:00 REVIEW & PREPARE Exploring new things #2	10:00 - 11:00 REVIEW & PREPARE Exploring new things #3	10:00 - 11:00 REVIEW & PREPARE Planning for the future			
10:15	10:15 - 11:15 MOVE Session						
10:30							
10:45							
11:00		Break (15 mins)	Break (15 mins)	Break (15 mins)			
11:15	Break (15 mins)	11:15 - 12:30 MOVE Session	11:15 - 12:30 MOVE Session	11:15 - 12:30 MOVE Session			
11:30	11:30 - 12:30 Key Worker Time						
11:45							
12:00							
12:15							
12:30	12:30 - 13:15 Lunch (45 mins)	12:30 - 13:15 Lunch (45 mins)	12:30 - 15:45 DO Session Picnic & Trip to the Museum	12:30 - 13:15 Lunch (45 mins)			
12:45							
13:00					13:00 - 13:30 Lunch (30 mins)		
13:15	13:15 - 14:30 REVIEW & PREPARE Exploring new things #1	13:15 - 14:15 REVIEW & PREPARE Communicating Pain		13:15 - 14:15 REVIEW & PREPARE 1:1 Key worker time - Progress planning	13:30 - 15:00 GRADUATION		
13:30							
13:45							
14:00							
14:15		Break (15 mins)		Break (15 mins)			
14:30	Break (15 mins)	14:30 - 15:45 DO Session Trying out activities #1		14:30 - 15:45 DO Session Trying out activities #2			
14:45	14:45 - 15:45 DO Session Helping hand activity						
15:00					Close at 15:00		
15:15							
15:30							
15:45	15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind	15:45 - 16:30 EXPLORE - Unwind			
16:00							
16:15							
16:30	16:30 End of day	16:30 End of day	16:30 End of day	16:30 End of day			

Legend: Weeks 1, 2, and 3 of the PPRP. The top of each week timetable shows the overarching concept of that week (e.g., Onboarding), while individual days are segmented into the interdisciplinary theme sessions (e.g., EXPLORE; DISCOVER). See Section 5.2 for further details.

Certificate Of Completion

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