FULL/LONG TITLE OF THE STUDY
Paediatric Chronic pain Clinic LOngitudinal Cohort (PiCCoLO) Study

SHORT STUDY TITLE / ACRONYM

PiCCoLO Observational Study

PROTOCOL VERSION NUMBER AND DATE

VERSION 0.4, 20 May 2024

RESEARCH REFERENCE NUMBERS

IRAS Number:	340388
SPONSORS Number:	R&D No: 24PC03
FUNDERS Number:	GOSHC W1167C

This protocol has regard for the HRA guidance.

PiCCoLO Study IRAS:340388

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 requirements.

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 publicly 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:
.....

Date:
...../...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature:

.....

Date:
22..../...5.../2024

Name: (please print):

SUELLEN WALKER

.....

LIST of CONTENTS

KEY STUDY CONTACTS

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Sponsor	Great Ormond Street Hospital **Phone**: 020 7405 9200 **Email**: NA **Fax**: NA
Funder(s)	Great Ormond Street Hospital Children's Charity **Phone**: (+44) (0) 20 3841 384 **Email**: supporter.care@gosh.org
Key Protocol Contributors	Study Co-ordinator (as above) Study Post-doctoral Research Associate: Dr Anna Fieldwalker; Anna.Fieldwalker@gosh.nhs.uk
Committees	C/o Great Ormond Street Hospital Charity

STUDY SUMMARY

Study Title	Paediatric Chronic pain Clinic Longitudinal Cohort (PiCCoLO)
Internal ref. no. (or short title)	PiCCoLO Observational Study
Study Design	Cohort observation – single site longitudinal
Study Participants	Children and young people (CYP) aged 8-18 years referred to the GOSH Chronic Pain Clinic
Planned Size of Sample (if applicable)	This large longitudinal cohort aims to recruit the majority of chronic pain referrals (estimate up to 200 participants per year, with the aim of 1000 participants in total)
Follow up duration (if applicable)	Up to 5 years post referral
Planned Study Period	10 years
Research Question/Aim(s)	Principal research question: What is the impact of chronic pain on general well-being in children and young people (CYP)? Principal objective: Utilise validated age-appropriate patient- and parent-report outcome measures (PROMS) and

	questionnaires to assess overall well-being (quality of life). Secondary outcomes will include pain intensity, pain interference with daily living, physical function, psychosocial and family function, and school function/attendance. Secondary research questions: - What is the trajectory of change in pain-related disability during and after management at pain clinic? - What are the clinical features of chronic pain experienced by children and young people (CYP) aged 8-18 years referred to the GOSH Chronic Pain Clinic? - What factors influence treatment response? - What is the economic burden of chronic pain in CYP?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN** **Great Ormond Street Children's Charity** 40 Bernard St, London WC1N 1LE
Great Ormond Street Hospital Children's Charity	GOSHC Award number W1167C

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The PiCCoLO Study will provide data related to usual care and outcomes following intermittent outpatient based multidisciplinary interventions (e.g., pain education, medication, physiotherapy, psychology) for chronic pain. This will provide usual care comparative data for the PIIPeR (Paediatric Intensive Interdisciplinary Pain Rehabilitation) study. PIIPeR is a trial within cohort study to evaluate outcome following a 3-week intensive rehabilitation programme, with eligible CYP aged 8-18 years randomised to early versus deferred intervention.

The PIIPeR Study Steering Group will also provide overall supervision of the PiCCoLO study. While the PiCCoLO Study will collate data from clinical records, and there will be no alterations in usual care, overall recruitment and data management will be reviewed by the broader PIIPeR Steering Group.

The Steering Group acts on behalf of the funder(s) and Sponsor.

Members of the PIIPeR Steering Group will include:

- PIIPeR Investigators: Dr Glyn Williams, Prof Suellen Walker, Prof Chris Eccleston
- Prof Navil Sethna, Clinical Director, Pediatric Pain Rehabilitation Center, Boston Children's Hospital (External Advisor)
- Prof Tonya Palermo, Center for Child Health, Behaviour and Development, Seattle Children's Hopsital (External Advisor))
- GOSH Divisional representative (Operation and Images) who will also provide a reporting line to the GOSH Executive.
- GOSHCC representative who will also supply a link to the GOSHCC Advisory Board
- Patient/public representatives to provide input relevant to patient experience and review progress with recruitment, patient/family satisfaction, and input/advice for further research protocols and applications.
- PIIPeR / Paediatric Pain Research Group Representative to report on progress and feedback to team.

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.

PROTOCOL CONTRIBUTORS

This protocol has been developed by the Chief Investigators and the study Postdoctoral Research Associate, in consultation with the external advisory group.

The PIIPeR study and the related collection of usual care data (now titled PiCCoLO) has been reviewed by the GOSHCC Research Assessment Panel. Neither the Sponsor nor Funder are involved in the design, conduct, data analysis and interpretation, manuscript writing, or dissemination of this observational study.

Participant information sheets have been reviewed for age-appropriateness and designed according to MCRN Young Person's Advisory Group guidance for patient information leaflets (www.mcrn.org.uk).

KEY WORDS: Paediatric; Chronic Pain; Child; Adolescent; Quality of Life; Parent/Carer

STUDY FLOW CHART

Time	Action	Outcome
Baseline – Visit 1 Usual Care	Consent & Initial Assessment following referral	Initial measurements taken
3 months – Usual Care	Usual Care Appt	Routine clinical data
6 months – Usual Care	Usual Care Appt	Routine clinical data
9 months – Usual Care	Usual Care Appt	Routine clinical data
12 months – Usual Care	Usual Care Appt	Routine clinical data
2 years – Usual Care	Usual Care Appt	Routine clinical data
3 years – FU1 (Optional)	Telephone interview	Follow-up questionnaire
5 years – FU2 (Optional)	Telephone interview	Follow-up questionnaire

PiCCoLO Study IRAS:340388

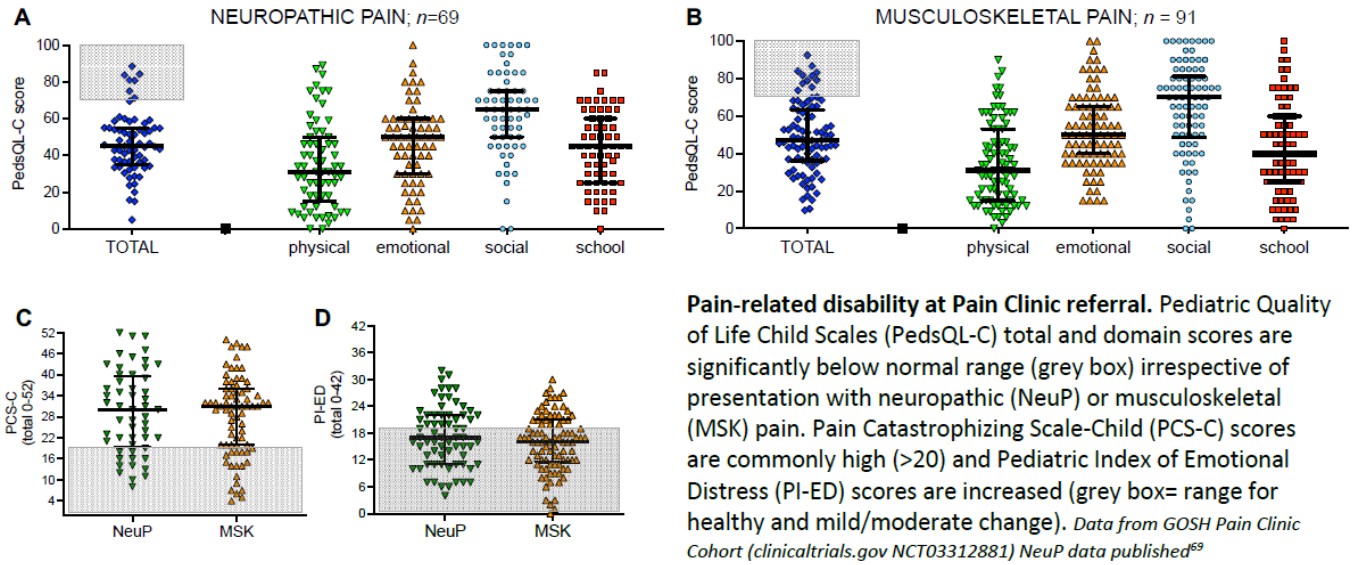
STUDY PROTOCOL

Paediatric Chronic pain Clinic Longitudinal cohort (PiCCoLO) - Observational Study

1 BACKGROUND

In England, 17.8% of adolescents self-report chronic pain at multiple body sites; a prevalence that is similar to other European centres and Canada (Gobina et al., 2019). More significantly, 5-6% of children and adolescents 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 (Huguet & Miro, 2008; King et al., 2011). In terms of the financial burden of pain, 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 £3,840 million/year (Sleed et al., 2005). In addition to direct health care costs, there are 'hidden' economic impacts related to parental time off work for care and hospital visits for children (ibid). In 2014, paediatric pain-related conditions in the USA were associated with health care expenditures of $11.8 billion (Groenewald et al., 2014). To date, evaluations of psychological interventions have focussed on clinical utility and efficacy rather than cost-effectiveness (Jacobsen et al., 2019). For pharmacological interventions, the lack of evidence-based guidelines (Eccleston et al., 2019) 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 (Battaglia et al., 2020; Groenewald et al., 2019; Groenewald et al., 2020).

Great Ormond Street Hospital NHS Foundation Trust is a world-leading research site, and our Chronic Pain Clinic is one of the largest UK paediatric services and one of few nationally commissioned services. Patients present with moderate-severe chronic pain that is associated with significant pain-related disability, irrespective of the underlying type of chronic pain. This is reflected by reduced quality of life with adverse effects on physical, emotional, social and school function. Many children report high levels of pain catastrophizing (i.e., tendency to worry and magnify symptoms, and feel helpless to control pain), and significant emotional distress with symptoms of anxiety and depression (Figure 1).



Pain-related disability at Pain Clinic referral. Pediatric Quality of Life Child Scales (PedsQL-C) total and domain scores are significantly below normal range (grey box) irrespective of presentation with neuropathic (NeuP) or musculoskeletal (MSK) pain. Pain Catastrophizing Scale-Child (PCS-C) scores are commonly high (>20) and Pediatric Index of Emotional Distress (PI-ED) scores are increased (grey box= range for healthy and mild/moderate change). *Data from GOSH Pain Clinic Cohort (clinicaltrials.gov NCT03312881) NeuP data published*[69]

Our current standard of care for children with chronic pain incorporates assessment by a multidisciplinary team (pain physician/paediatrician, clinical nurse specialist, physiotherapist, psychologist) that leads to a biopsychosocial formulation and management plan that is discussed with patients and families. Interventions are delivered and reviewed via intermittent outpatient appointments (face-to-face and/or video plus telephone follow-up), and may include Pain Education Sessions, medication, home exercise programmes or

more intensive physiotherapy rehabilitation, and clinical psychology interventions. We liaise with local care teams, and with school and social services, as required.

Improvements in quality of life (PedsQL total score) 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) (Figure 2). However, there is significant variability at both timepoints, and for children with severe pain-related disability, gains with this intermittent approach can be slow and/or inadequate. Proportions of patients achieving a PedsQL total score of 66 (defined as a clinically significant cutoff (Randall et al., 2018)) reveals the following proportions: 16% maintained PedsQL score > 66 at both time points; 37% improved to scores >/= 66; 48% did not attain the cutoff of 66.

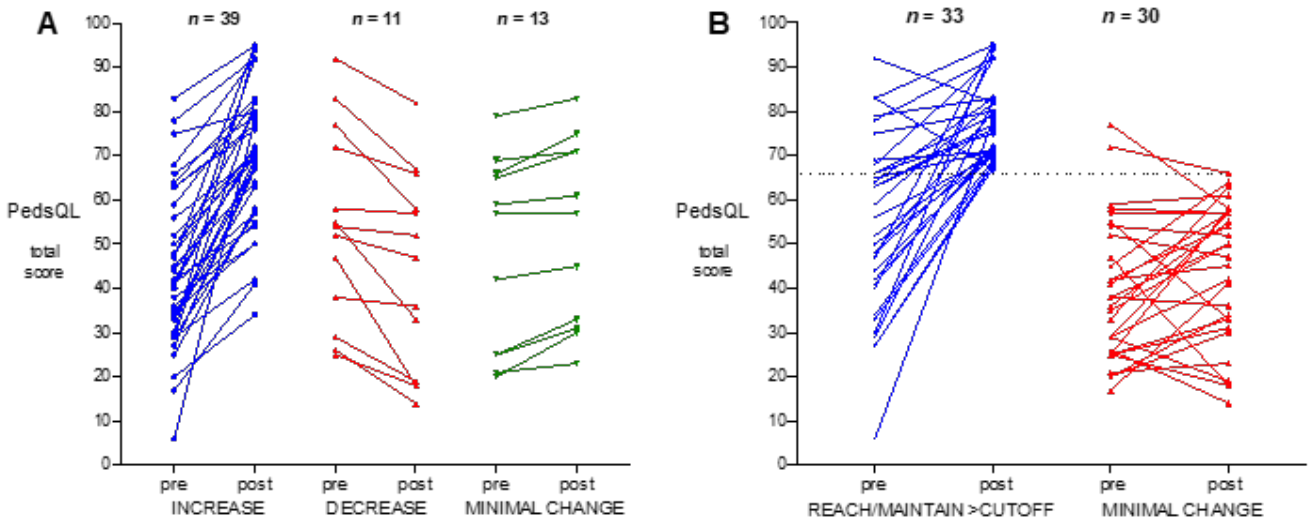


Figure 2. Quality of life (PedsQL-Child Core Domain V4) total score reported by chronic pain patients at referral and on discharge for GOSH Chronic Pain Clinic.

There is also a paucity of data related to longer-term outcomes, or if any gains achieved during chronic pain clinic management are maintained following discharge. Recent telephone follow-up (Audit No: 2865; registered 8/6/2020) of adolescents (mean age 13yrs, 63% female, n=59) with complex regional pain syndrome managed at GOSH Pain Clinic found that half reported chronic pain episodes at least weekly or monthly following discharge, and this was the same in 23% and worse in 10% (average 4 years post referral). While 70% reported no or minimal impact of pain on education or work, over half reported an ongoing impact of pain on mood. These data highlight the need for more detailed evaluation of the trajectory of pain and related symptoms for a longer period post discharge, and across a range of different types of pain and underlying conditions.

2. RATIONALE

Chronic paediatric pain has significant adverse effects on health, physical function, emotional well-being and school attendance. There are additional impacts on family function, and costs associated with parental time of work for care or hospital visits, and health care utilisation. Documenting the wide-ranging impact of chronic paediatric pain is needed to understand the complexities of this condition, and also highlight the need for adequate health care resources.

Factors that influence outcome and treatment response have not been systematically studied in our chronic pain cohort. A large cohort with prospectively collected data (i.e. clinical history, pain classification, demographic data, pain interventions, and patient- and parent-reported outcome measures) is needed to

assess factors that contribute to variance in treatment response. Further understanding of the impact of chronic pain is needed to inform treatment and reduce the economic burden of chronic pain.

We wish to recruit all children aged 8-18 years attending their first appointment at GOSH Pain Clinic to a longitudinal cohort study. Clinical and demographic data, medication and health care utilisation, questionnaire results collected at pain clinic, and details of pain treatment/interventions will be entered into a database. In addition, participants will be able to opt in or out of additional follow-up and completion of questionnaires at 3 and 5 years following their initial assessment, at which point many participants will have been discharged from the service. The knowledge generated by this observational study will contribute to:

- ongoing review of our current practice within the context of a prospective research study, which will build on our previous work utilising audit methodology to retrospectively retrieve patient outcome data
- improved understanding of the impact of chronic pain and response to different types of intervention
- identifying potential factors associated with poor outcome that may be targets for intervention and quality improvement projects

3 THEORETICAL FRAMEWORK

A longitudinal observational cohort study is an appropriate design to describe and quantify the type and impact of chronic pain in CYP, and the degree and duration of change throughout usual care. It is routine practice at GOSH Pain Clinic to collect Patient- and Parent-Reported Outcome Measures (PROMs) at each clinic appointment. These are uploaded into the electronic medical record (EPIC). Results are reviewed by the multidisciplinary clinical care team and used to: i) assess pain and pain-related disability; ii) inform a biopsychosocial formulation and management plan; and iii) collection at subsequent appointments facilitates monitoring of treatment response.

We now wish to prospectively collect clinical data, PROMs scores, and information regarding interventions (type, frequency, how delivered) throughout the usual 2-year clinical management pathway at Chronic Pain Clinic. While selected data have been previously retrieved retrospectively for clinical audits and annual reviews of practice, prospective data collection in as many patients as possible will facilitate more comprehensive analyses. This will allow us to establish trajectories of pain-related disability, improvement, and/or response to treatment, and to benchmark this against other centres.

This proposal aligns with the aim of GOSH NHS Foundation Trust to be a research hospital, and to include as many children as possible in studies. Enrolment in this study will not alter usual clinical care, and we anticipate high levels of recruitment. In addition, patients and families will have the option to consent or decline follow-up following discharge from pain clinic (3 and 5 years post initial referral) and to provide additional details regarding health care utilisation and family financial burden of care.

4 RESEARCH QUESTION/AIM(S)

1. What is the impact of chronic pain on general well-being in CYP?
2. What is the trajectory of change in pain-related disability during and after management at pain clinic?
3. What are the clinical features of chronic pain experienced by children and young people (CYP) aged 8-18 years referred to the GOSH Chronic Pain Clinic?
4. What factors influence treatment response?
5. What is the economic burden of chronic pain in CYP?

4.1 Objectives

1. Utilise validated age-appropriate patient- and parent-report outcome measures (PROMS) and questionnaires to assess overall well-being (quality of life). Secondary outcomes will include pain intensity, pain interference with daily living, physical function, psychosocial and family function, and school function/attendance.
2. Evaluate the change in PROMs with time by collecting longitudinal data from each clinic visit, and extend outcome reporting to include questionnaires at 3 and 5 years post referral for participants consenting to longer-term follow-up.
3. Identify and classify the type, distribution and duration of chronic pain reported by CYP aged 8-18 years of age referred to the GOSH Chronic Pain Clinic.
4. Explore the relationship between pain classification, pain-related disability and response to treatment interventions (pharmaceutical/multidisciplinary/intervention programmes etc.)
5. Explore the cost of chronic pain on healthcare use (GP and hospital visits; medication use; investigations; interventions) and the family as a whole (e.g. economic burden of travel, parental time off work).

4.2 Outcome

Our over-arching aim is to identify current best practise and utilise data from this large longitudinal cohort to inform ongoing usual care and improve long-term outcomes for children with chronic pain.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

This will be an **observational** study to explore change in patient-reported pain, overall well-being, emotional and physical function, and educational attainment over time. The research team will collect usual care data through EPIC, the electronic patient record system used at GOSH. This will include: demographics; type, intensity and duration of pain; diagnostic category; clinical details; previous investigations; additional assessments such as quantitative sensory testing or investigations performed as part of routine pain clinic care; patient- and parent-reported outcome measures and questionnaires; and interventions received for pain (pain education, medication, physiotherapy and/or psychology interventions).

Participants may also opt-in to further follow-up involving collection of data on pain, interference with activity due to pain, and healthcare use, at 2 additional time-points (three and five years following their initial assessment at the pain clinic). The follow-up interviews will involve completion of a Case Report Form with the research team, either online or by telephone.

Data Analysis:

All participants will be allocated an anonymised Study ID. A linking file which includes the participant's hospital number and the Study ID will be kept in a separate locked filing cabinet in a secure location that requires GOSH ID badge swipe access.

Data will be entered into a cloud-based REDCap Database. This will be setup with the Digital Research Environment (DRE) team at GOSH. The DRE team manages a digital research platform supplied by Aridhia and provides secure access to data recorded in the Electronic Patient Record (EPIC) at GOSH. This allows for data management, visualisation and analysis in research projects. Trained and approved researchers who have up-to-date GCP certification are given an access code for the database, and data will not leave GOSH. Data will be stored securely for twenty-five years.

6 STUDY SETTING

The study will recruit CYP aged 8-18 years attending the GOSH Chronic Pain Clinic, which currently receives over 240 referrals per year. A member of the clinical care team will identify potential participants and a Parent/Carer Information Sheet and the appropriate age range Participant Information Sheet will be sent with the patient appointment letter, or to be received at least 2 days prior to the first appointment. This will be sent via post and MyGOSH (online patient portal) as per current usual care. The clinical data and PROMs that will be assessed in this study will be collected and stored via EPIC at each patient visit. If the patient consents to follow-up assessment at 3 and 5 years following their initial assessment, a Case Report Form will be completed with the researcher via telephone or online interview (depending on participant and parent/carer preference).

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

The study aims to recruit all CYP aged 8-18 who are referred to the GOSH Chronic Pain Service.

7.1.1 Inclusion criteria

- Children and young people aged 8-18 years with chronic pain (>3 months duration) referred to GOSH Chronic Pain Clinic.
- Males and females. If participants are over 16, self-reported gender will also be collected if this option is available and has been entered by the participant on EPIC; participants of all genders will be included.
- Willing and able to provide written informed Participant consent/assent and Parental consent.

7.1.2 Exclusion criteria

- Unwilling/unable to provide written informed Participant consent/assent and Parental consent.
- Outside of the stated age range (8-18 years).
- If the parent/carer is unable to understand English, consent will be obtained only if a suitable interpreter can be sourced in line with usual clinical care. CYP who are unable to speak English or who are only managing school at a level less than usual for an 8-year old will be excluded as current versions of PROMs on EPIC are not validated at younger ages and are not currently available in multiple languages.

7.2 Sampling

7.2.1 Size of sample

We wish to recruit all participants who fulfil the criteria and to collect their usual clinical data, aiming for at least 1000 participants. We wish to include as many of our paediatric pain population as possible to provide a representative and inclusive sample. The large sample size will have sufficient power to include a larger number of variables in the analysis, compare trajectories of response, and evaluate predictors of persistent pain and disability.

7.2.2 Sampling technique

The study will employ convenience sampling with recruitment open to all eligible participants referred to the GOSH Chronic Pain Clinic. This ensures a wide spread of participants while also only approaching those in the population who will potentially benefit from this area of research.

7.3 Recruitment

7.3.1 Sample identification

The clinical team will identify participants through the usual referral process. Only members of the existing clinical care team will have access to referral information and electronic patient records on EPIC prior to the clinic appointment. We will not employ Participant Identification Centres or publicity for recruitment.

The well-established electronic patient record system, EPIC, will be used to identify scheduled appointments, retrieve the relevant information, and to deliver the appropriate PROMs. As this study does not involve any visits outside of the participants' usual care, there are no payments necessary for additional research-related travel expenses.

7.3.2 Consent

Parent/Carer Information Sheets and age-appropriate Participant Information Sheets (8-11 years, 12-15 years, or 16-18 years) will be prepared in accordance with MCRN and HRA guidance. The dates when the Parent/Carer and Participant information sheets have been sent and received will be recorded in the medical/case notes/source documents. Adequate time (at least 48 hours) will be given for review and consideration by the participant and parent/carer of Participant and Parent/Carer Information Sheets before taking part.

Potential participants who are accepted into the service, and have a pain clinic appointment scheduled, will be approached at this appointment to determine if they have received the relevant Parent and Participant Information Sheets. The Chief Investigators or designated research team member 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 patient data being used;
c) answer questions related to the study.

Written informed parental consent and participant consent (age 16 years and over) or assent (< 16 years age) will be obtained prior to participation in the study. Procedures to assess capacity of participant consent will be assessed according to NRES guidance and documented in study documents. The person taking consent will be GCP trained, suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks Record.

The Investigator or designee will explain that participants are under no obligation to enter the study and that parents or participants can decline consent without having to give a reason. No patient data will be extracted for study observation prior to the parent giving consent and the participant giving consent/assent by signing the consent forms.

A copy of the signed informed consent/assent forms will be given to the participant and parent/carer(s). The original signed forms will be retained in the study file at site and a copy placed in the medical/case notes/source documents.

The participants Study ID and date of birth will be entered into a REDCap database, and an alert to the research team will be triggered if the participant reaches a new age bracket for assent or consent. Participants who reach 12 years of age will be asked to complete an age-matched assent form, and participants who reach 16 years will be asked to complete a consent form. They will also receive an updated age-appropriate participant information sheet.

Participants and parent/carers will have the option to withdraw from the study at any point without this affecting usual clinical care. Data already gathered at the point of withdrawal will be retained. This is in order to protect the validity of the research and is permissible as an exemption to data subject rights under GDPR.

7.3.3 End of Study

For individual participants, the duration of the study will be up to five years following referral to GOSH Pain Clinic. This will encompass: i) usual care throughout attendance and management at Pain Clinic (typical usual care pathway is 2 years); ii) telephone or online questionnaires administered by the research team at 3 and 5 years post referral for participants and families who consent to longer term follow-up; and iii) potential shorter duration if participants or families withdraw consent.

The PiCCoLO study aims to collect data from as large and representative a sample of Pain Clinic patients as possible. Numbers for recruitment, complete data sets, and longer-term follow-up will be reviewed and discussed at 6-monthly Trial Steering Committee meetings. Preliminary descriptive analyses will be performed after 2 and 4 years. Throughout the 9-year funding of the PIIPeR Programme, recruitment to PiCCoLO will continue for 6 to 7 years, with the aim of achieving a sample size of 1000 completing usual care at GOSH Pain Clinic.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

The study does not involve any procedures outside of usual care and subsequent follow-up. All questionnaires given during usual care are reviewed and delivered by the clinical care team. No new types of questionnaires will be given during post-discharge optional follow-up.

Regarding safeguarding issues, the management plan already in place with usual care and multidisciplinary assessment will apply. Outcome measures will be reviewed as part of clinical care and any significant findings (e.g., high levels of emotional distress) will be managed as per usual care. If the participant or parent/carer raises concerns with the research team about pain while they are being managed by the Chronic Pain Clinic, they will be asked to contact their Pain Clinical Nurse Specialist by phone or via MyGOSH. If participants and/or parent/carer(s) who agree to longer-term follow-up raise issues about ongoing pain when the child is no longer a patient at GOSH, we will suggest contacting their GP or current health care providers for advice, or accessing the self-management resources that are sign-posted by the Pain Team as part of usual care.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Prior to the start of the study, a favourable opinion will be sought from the HRA and appropriate research ethics committee, and local R&D approval will be confirmed prior to any participant recruitment. The study protocol and all other supporting documents including any agreed amendments, will be documented and submitted for ethical and regulatory approval as required. All correspondence will be retained. Within 90 days after the end of the trial, the research team will ensure that the main REC are notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study. The CI will prepare and a summary report of the study, which will be submitted to the main REC within 1 year after the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
The CI will supply the Sponsor with a report of the study and a copy of the report submitted to the main REC, within 1 year after the end of the study.

Regulatory Review & Compliance

See above.

Amendments

The Chief Investigator and research team will ensure that all amendments gain the necessary approvals. The CI and sponsor will decide whether the amendment is substantial or non-substantial. If the sponsor wishes to make a

substantial amendment to the REC application or the supporting documents, they will submit a valid notice of amendment to the REC for consideration. Amendments will not be implemented prior to receipt of the required approval(s), and the appropriate REC and NHS R&D will be informed of any non-substantial or substantial changes needed. The amendment history will be tracked to identify the most recent protocol version by updated and consistent naming on all documents (version number + date).

8.3 Peer review

The proposed study has undergone extensive peer review following submission to a commissioned research call by Great Ormond Street Hospital Charity. Feedback from the Research Assessment Panel and a subsequent External Advisory Group have informed study design and conduct for the overall PIIPeR Study that incorporates the PiCCoLO usual care group.

8.4 Patient and Public Involvement and Engagement

The Lancet Adolescent and Child Health Commission included patient and public representatives as co-authors and identified goals for "Delivering transformative action in paediatric pain." (Eccleston et al., 2021). 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 to document the impact of pain and response to treatment; 'make pain understood' by focussing on the aim of better understanding paediatric pain outcomes and trajectories, with parallel research studies investigating underlying mechanisms; and 'make pain better' by providing foundational data to inform improvement of pain care.

The current funding is based on a family's lived experience of chronic pain in childhood and the benefit achieved with research on pain in the outpatient clinical setting. Chosen assessment tools encompass mandatory, important, and research domains within the core outcome set for paediatric chronic pain trials and longitudinal clinical care developed with input from health care providers, adolescents with pain, and parents (Palermo et al., 2021). Participants and families will have access to anonymised results of the project through regular reports and publication of results in open access journals.

Participant Information Sheets incorporate HRA recommended transparency wording, and are informed by PISs that were used successfully in previous studies recruiting children and young people from GOSH Pain Clinic (Ref: 17/WM/0306; Approval: 23-8-2017). Patients with chronic pain managed by the Pain Service at GOSH, and the GOSH Young Peoples Advisory Group have contributed to PPIE activities related to pain research. This has been led by Dr Helen Laycock, a Pain Consultant and member of the clinical team who has formal training in PPIE. GOSH YPAG emphasised the importance of reassurance in alleviating worries when taking part in research, and highlighted that information is key. The lack of peer support for young people with chronic pain was a recurring theme in semi-structured interviews and in those attending our Pain Education Sessions. Our Postdoctoral Research Associate (Dr Fieldwalker) has discussed plans for ongoing PPIE activities with Dr Laycock and the GOSH YPAG co-ordinator This will include the preparation of newsletters summarising anonymised group results. Participants and families will have the option to supply contact details if they wish to receive newsletters.

8.5 Protocol compliance

Any protocol deviations will be recorded on relevant forms and immediately reported to the Chief Investigator and Sponsor; with mitigations put in place to prevent recurrence.

8.6 Data protection and patient confidentiality

The Principal Investigator will be the data custodian. All members of the research team will have received up-to-date data security, GDPR, and information governance training, compliant with 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 in a separate locked filing cabinet in a secure location that requires GOSH ID badge swipe access. Patient data from their referral through

to discharge 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 Digital Research Environment (DRE) team at GOSH. 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. Electronic data being used for preparation of presentations and manuscripts will be stored in encrypted, password-protected computers within GOSH. We will comply with the requirements in the R&D Data Protection Registration Form. After study completion, pseudonymised data will be retained in compliance with the Data Retention Policy and principles of the Data Protection Act. Our Research Ethics submission will include seeking consent to combine results with future studies, and data will be stored for a minimum 25 years.

8.7 Indemnity

Great Ormond Street Hospital NHS Foundation Trust (study sponsor) holds insurance against claims from participants for injury caused by their participation in the observational study. As this study is being carried out in a hospital, the hospital continues to have duty of care to the participant of the study. Participants may be able to claim compensation for injury caused by participation in this study 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 will provide clinical negligence insurance cover for harm caused by their employees. As this is an observational study, it does not involve any process beyond the participant's usual care, other than optional follow-up interviews.

Parent Information Sheets will include the following information:

If you have a concern about any aspect of this study, you should ask to speak to the Chief Investigators (Professor Suellen Walker or Dr Glyn Williams) who will do their best to answer your questions. It is highly unlikely that taking part in this study could harm you and/or your child.

Every care will be taken in the course of this study. However, in the unlikely event that you (or your child) are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (Great Ormond Street Hospital) negligence, then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Dr Suellen Walker who is the Chief Investigator for the research and is based at Great Ormond Street Hospital, who will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you or your child have been approached or treated by members of staff, or about any side-effects experienced due to participation in the research, the normal National Health Service complaints mechanisms are available to you. You can contact the Patient Advice and Liaison Service (PALS) at Great Ormond Street Hospital. Email: pals@gosh.nhs.uk Tel: 020 7829 7862

8.8 Access to the final study dataset

Only the research team will have access to the final full dataset. As a single-centre study, access to the data will be limited to the GOSH research team for this project. 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 as an option i.e., all participants are given the option to withhold consent for their anonymised data being used in any secondary analysis or being included with future research studies.

9 DISSEMINIATION 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 www.clinicaltrials.gov (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 additional follow-up which requires contact details (e.g., email address or telephone number), 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

Authorship will be decided in accordance with the ICMJE defined authorship criteria.

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11. APPENDICES

11.1 Appendix 1- Required documentation (see other attachments)

SW CV

GW CV

AF CV

PIS – Parent/Carer

PIS – Child (8-11, 12-15, 16+)

Assent Form – Child (8-11, 12-15)

ICF – Parent/Carer

ICF – Participant 16+

CRFs

Withdrawal Forms

Invitation Letters

GDPR Information

Patient Logsheet

11.2 Appendix 2 – Schedule of Procedures (Example)

Procedures	**Visits**						
	Screening (>2 days prior to appt)	**Baseline** (First clinic appt; Visit 1)	**6mo** (Visit 2)	**1y** (Visit 3)	**2y** (Expected Discharge)	**3 years**	**5 years**
Participant Information Sheets	X						
Informed consent/assent		X	(x)	(x)	(x)	(x)	(x)
Demographics		x					
Medical history		x				x	x
PROMs		x	x	x	x	x	x
Follow-up Interview (telephone / online)						x	x

(x) = conditional i.e., if CYP reaches new age bracket

13.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made