

HRA PROTOCOL COMPLIANCE DECLARATION

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

STUDY TITLE

FULL/LONG TITLE OF THE STUDY

Development of an Online, Interdisciplinary Intervention for Paediatric Chronic Pain Management

SHORT STUDY TITLE / ACRONYM

Online Intervention for Paediatric Chronic Pain Management

PROTOCOL VERSION NUMBER AND DATE

Version 1.5 (12/06/2019)

RESEARCH REFERENCE NUMBERS

IRAS Number: 253044

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SIGNATURE PAGE

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

Date:

.....
Name (please print):

.....
Position:

Chief Investigator: Professor Christina Liossi

Signature:

Date:

.....
Name: (please print):

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GENERAL INFORMATION

KEY STUDY CONTACTS

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Committees	N/A

STUDY SUMMARY

Study Title	Development of an Online, Interdisciplinary Intervention for Paediatric Chronic Pain Management
Internal ref. no. (or short title)	Online Intervention for Paediatric Chronic Pain
Study Design	Qualitative methods only. Semi-structured interviews.
Study Participants	The study aims to recruit adolescents (12 to 17 years) with either cancer-related or non-cancer chronic pain, from Great Ormond Street Hospital (GOSH) and Royal Marsden Hospital (RMH), with additional recruitment from patient organisations and charities, and via social media. Parents of adolescents with chronic pain of either type will also be recruited.
Planned Size of Sample (if applicable)	<p>The study aims to recruit approximately 15 participants per group at GOSH:</p> <p>Children with chronic pain (n = 15)</p> <p>Parents of children with chronic pain (n = 15),</p> <p>Approximately 10 participants per group will be recruited from RMH:</p>

	<p>Children with cancer-related chronic pain (n = 10)</p> <p>Parents of children with cancer-related chronic pain (n = 10),</p> <p>Community:</p> <p>Children with chronic pain (any type) (n = 5)</p> <p>Parents of children with chronic pain (n = 5)</p> <p>The overall sample size projected is a group of 60 stakeholders.</p> <p>Analysis will be ongoing and recruitment will continue up until the point of saturation (Guest, Bunce & Johnson, 2016).</p>
Follow up duration (if applicable)	N/A
Planned Study Period	June 2019 – March 2021
Research Question/Aim(s)	<p>The current study aims to gain an overall insight as to what adolescents and their parents want to be included in an intervention for paediatric chronic pain.</p> <p>The primary research question is:</p> <p>What content and features do young people with chronic pain, and their parents, want to see in an online pain management intervention?</p>

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
University of Southampton	AHW is funded by a University of Southampton Jubilee PhD scholarship.
Great Ormond Street Hospital for Children NHS Foundation Trust	Participating clinicians from GOSH will identify potential participants to the core research team.
The Royal Marsden NHS Foundation Trust	Participating clinicians from RMH will identify potential participants to the core research team.

ROLE OF STUDY SPONSOR AND FUNDER

The University of Southampton is sponsor and funder of this research as part of a PhD Jubilee +3 research studentship for Miss A. Hurley-Wallace.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

N/A

PROTOCOL CONTRIBUTORS

Miss Anna Hurley-Wallace has developed this protocol under the guidance of Prof. Christina Liossi and Dr Daniel Schoth. Miss Lauren Johnstone, Dr Daniel Schoth, Dr Glyn Williams, Miss Suzanne Lilley, and Dr Anna Karenia Anderson have also contributed to this protocol.

KEY WORDS:

Paediatric Chronic Pain, Paediatric Pain Management, Online Intervention, Interdisciplinary, Cognitive Behavioural Therapy, Qualitative Research

STUDY FLOW CHART


STUDY PROTOCOL

1

BACKGROUND

Chronic pain is most commonly defined as pain that lasts for a period of longer than three months, (Steingrimsdottir, Landmark, Macfarlane & Nielsen, 2017; Treede et al., 2015). Prevalence rates for children and adolescents suggest that chronic pain is experienced by up to 15-30% of the population, with an estimate of up to 1-3% of the paediatric population experiencing severe and disabling chronic pain (Eccleston, Bruce & Carter, 2006). Prevalence rates for different chronic pain conditions vary across the literature, where chronic headache appears to be the most common paediatric chronic pain condition; reported prevalence ranges from 8% to 83% (King et al., 2011). Across paediatric populations, females are more prone to chronic pain than males (King et al., 2011).

Chronic pain in paediatric cancer survivors, often described as 'cancer-related pain', is usually conceptualised differently compared to chronic pain of other aetiologies, as reflected in the recent ICD-11 classification guidelines (Treede et al., 2015). A systematic review of pain in adolescents with leukaemia or brain tumour found that chronic cancer-related pain may be procedure-related, treatment-related, or associated with the cancer itself, and is likely to persist chronically after treatment completion(Olson & Amari, 2015). A recent systematic review of chronic pain prevalence in childhood cancer survivors has estimated prevalence in paediatric populations between 3% and 50%, dependent on the type of cancer, and treatments received (Hurley-Wallace, Schoth, et al., 2018). The review noted that very few studies have investigated chronic cancer pain specifically in paediatric and adolescent samples. A theoretical model of chronic cancer pain has recently been developed by Heathcote and Eccleston (2017), which focuses on differentiating factors between chronic cancer and non-cancer pain, such as fear of recurrence, in cancer survivors.

Chronic pain conditions can severely affect the lives of young people and their families. Children and adolescents with chronic pain report substantially worse quality of life than their healthy peers in domains of physical and psychosocial functioning, poorer performance in school and relationships with peers (Dick & Riddell, 2010; Forgeron et al., 2010; Logan, Simons, Stein & Chastain, 2008; Varni, Limbers & Burwinkle, 2007). The effects of paediatric chronic pain affect both the family unit and individual family members. Children with chronic pain and their families report worse behaviour control, family disturbances, family cohesion and conflict, and organisational structure than families without children with chronic pain (Lewandowski, Palermo, Stinson, Handley & Chambers, 2010). Parents of children with chronic pain also report suffering higher levels of anxiety and depression than parents of healthy children, as well as feelings of helplessness and a lack of control (Palermo & Eccleston, 2009).

Currently, treatment for paediatric chronic pain typically occurs in outpatient settings, and is usually focused on providing multimodal treatment, which can include physiotherapy, medication and cognitive behavioural therapy (Miro, McGrath, Finley & Walco, 2017). The use of interdisciplinary interventions for the treatment of paediatric chronic pain is supported by a recent review of treatments for paediatric musculoskeletal pain, which highlighted the lack of evidence supporting the use of pharmacologic treatment alone. The review also affirmed the strong evidence base for psychological treatment, and the promising yet limited support for the role of physiotherapy (Caes, Fisher, Clinch &

Eccleston, 2018). Interventions for paediatric chronic pain that combine two or more disciplines have been found to be effective in improving pain, disability, and emotional functioning; however, systematic reviews have also emphasised the substantial heterogeneity in the literature evaluating such interventions (Hechler et al., 2015; Liossi, Johnstone, Lilley, Williams & Schoth, 2018). Interdisciplinary interventions are considered the “gold standard” treatment for paediatric chronic pain.

Despite the apparent success of interdisciplinary interventions, there are several barriers to successful interdisciplinary care in paediatrics, including time taken out of school to travel to clinics, and associated financial concerns (Bender, Radhakrishnan, Diorio, Englesakis & Jadad, 2011; Caes et al., 2018), and poor accessibility in rural areas (Elgar & McGrath, 2003). A possible solution would be remote delivery over the internet.

Psychology-based interventions have been indicated to be effective when delivered remotely. A systematic review by Fisher, Law, Palermo, and Eccleston (2015) investigated studies that tested the efficacy of remotely delivered psychological interventions for children and adolescents with chronic pain. This review included eight studies utilising the internet, CD-ROMs and audio tapes to deliver Cognitive Behavioural Therapy (CBT) interventions to children. Five studies investigated patients with chronic headache, two studies investigated mixed pain conditions (headache and other chronic pain presentations), and one investigated juvenile idiopathic arthritis. The authors split the papers into headache related pain conditions and “mixed pain conditions”. Results of the review illustrate that remotely delivered therapies can effectively reduce headache severity post-treatment, and can reduce pain intensity post-treatment for mixed pain conditions in children. The review also notes a lack of research in the area. Another meta-analytic review of randomised controlled trials assessed the effects of psychological interventions on child and adolescent chronic pain, and found that interventions delivered via computer-based applications were as effective in reducing chronic pain and disability as face-to-face treatment (Palermo, Eccleston, Lewandowski, Williams & Morley, 2010). However, this evaluation is based on only two trials of computer-based applications for paediatric chronic pain management; hence, further research trials are needed to support the efficacy of online interventions.

A key CBT-based intervention that has been developed and tested for the online management of paediatric pain is Web-MAP2 for adolescents aged 11 to 17 years (Palermo et al., 2016). The intervention is travel-themed, and includes modules on pain education, recognising stress and negative emotions, deep breathing and relaxation, implementing coping skills at school, cognitive skills, sleep hygiene and lifestyle, staying active, and relapse prevention. The parents of the participants complete modules relating to pain education, recognising stress and negative emotions, operant strategies, modelling, sleep hygiene and lifestyle, communication, and relapse prevention. The intervention also includes a symptom e-diary.

Research has also evaluated mindfulness and acceptance therapy as part of the internet-delivered “Teens taking charge: Managing arthritis online” intervention (Stinson et al., 2010). The intervention included components such as managing symptoms, distraction techniques, and information on exercise and nutrition. Taken together, outcomes from the WebMAP2 and “Teens taking charge” interventions support the efficacy of internet delivered self-management programs for significantly reducing pain intensity post-treatment (Palermo et al., 2016; Stinson et al., 2010).

There is currently a lack of literature investigating internet-delivered interventions for paediatric chronic cancer-related pain. However, one evidence-based mobile application ('app'), which targets treatment-related acute cancer pain in children and adolescents, have been developed and evaluated; Pain Buddy (Fortier, Chung, Martinez, Gago-Masague & Sender, 2016).

Pain Buddy (Fortier et al., 2016) focuses on self-management techniques and was developed with a multidisciplinary task force of psychologists and healthcare professionals. It uses social learning principles to encourage practice of self-management techniques at home. The app includes an e-diary, guided interventions such as breathing techniques, and a reward system in which patients can "buy" new avatars. A pilot test of the app suggests that children considered it useful, and were encouraged to use non-pharmacological pain management techniques, such as social support, instead of analgesics. While preliminary, these results suggest that online interdisciplinary interventions may encourage effective cancer pain management in children.

A key critique of the aforementioned interventions is that they do not consider adolescent or parent views in the intervention development process, which may be key to understanding patient perspectives, and producing improved tools (Higgins et al., 2018). Involvement of stakeholders in the design and development process also forms part of the Person-Based approach to intervention development, which outlines the importance of qualitative insights in health-related behaviour change interventions for improving health-related outcomes (Yardley, Morrison, Bradbury & Muller, 2015). There is no evidence to indicate that a Person-Based or user-centred approach was used to inform the development of Web-MAP2 or Teens taking charge. To date, only one study by Stinson et al. (2014) has considered adolescent views in the development of an intervention for paediatric chronic pain (iCanCope with pain). Twenty-three adolescents (aged 14 to 18 years) were recruited from two pediatric chronic pain clinics in Ontario. The study used focus groups with adolescents and healthcare professionals working in chronic pain, which were then analysed thematically to inform initial content and design (iCanCope is yet to be trialled).

Whilst preliminary evidence suggests that psychology-based online pain management interventions in paediatrics can be successful in managing a variety of types of chronic pain, (Fisher et al., 2015; Palermo et al., 2010) the interventions that have been developed do not mirror the multimodal treatment that is delivered in practice, and have not considered stakeholder views in their development. These systematic reviews of interventions, as well as a recent review of researcher-led eHealth tools for pain assessment and management (Higgins et al., 2018) all note that more research is needed into online pain management in paediatrics. Particularly new interventions could consider including elements of physiotherapy (Caes et al., 2018), and whilst psychological elements may be successfully delivered online (e.g. Fisher et al., 2015), a balance between the disciplines may be essential to the success of a new online intervention for paediatric chronic pain.

2 RATIONALE

Adolescents are spending increasingly more time online; 12-15 year olds may spend on average 21 hours a week online (Ofcom, 2017); hence, it is unsurprising that recent review notes some preferences for e-health in paediatrics (Higgins et al., 2018). Additionally, whilst findings are

preliminary and long-term efficacy is unclear, online psychological interventions for paediatric chronic pain can be effective in improving pain-related outcomes (Fisher et al., 2015; Palermo et al., 2010).

Current clinical practice utilises interdisciplinary methods to manage paediatric pain (Miro et al., 2017), and future online interventions should reflect this. There is also no current online interdisciplinary pain management intervention, which includes a module specifically targeting cancer-related chronic pain. Additionally, of the interventions that have been developed, the vast majority do not consider the views of adolescents and parents as part of the development process. Engagement of stakeholders from the earliest stage of the development process can help researchers better understand patient priorities and perspectives, and therefore develop improved tools (Higgins et al., 2018).

Stinson et al. (2014) considered adolescent views in the development of an intervention for paediatric chronic pain, in-line with the Person-Based Approach to intervention development (Yardley et al., 2015). However, this approach has not been undertaken to develop an online intervention for paediatric chronic pain management in the UK. Research has noted the importance of grounding health interventions in the context of the cultural system that relates to the patients who will be using the intervention. This may help to achieve sustainable change resulting in positive health outcomes (Airhihenbuwa, Ford & Iwelunmor, 2014). The NHS is a key part of health care system in the UK; hence, it is important that the intervention being developed is grounded in this context, and matches the standards of care and mode of delivery that patients would receive in NHS clinics.

The current study aims to gather adolescent and parental views about what interdisciplinary content should be included in an online intervention for chronic pain management, what this should look like, and gain an overall insight as to what adolescents and their parents want from an intervention for paediatric chronic pain management.

The wider programme of research, that this study is a part of, aims to develop, implement and evaluate the efficacy of an online intervention for paediatric pain management. The ultimate ambition of this intervention, if evaluated as efficacious, is to make it freely available via the NHS, such that it will be easily accessible to paediatric pain patients. The collaborating NHS clinicians contributing to this research will help to ensure that the intervention will mirror the multimodal treatment for paediatric chronic pain that is used in practice. This collaboration, alongside the user-centred approach to intervention development, may optimise intervention design and adoption by stakeholders (Higgins et al., 2018).

3 THEORETICAL FRAMEWORK

This study is the first step in the development process for an online intervention for paediatric chronic pain management. The Person-Based approach will inform the overall development of the intervention. The first stage of this approach highlights the importance of developing online intervention content with insights from stakeholders in order for interventions to be effective (Yardley et al., 2015); hence the current study investigates the views of children and adolescents, as they are key stakeholders for this intervention. Recent review of e-health tools for pain assessment and management clarifies that these insights are important to understand stakeholder priorities and

perspectives, and thereby develop a more effective intervention (Higgins et al., 2018). However, in the process of co-design, whilst stakeholder views are important, there is recognition that the expertise of professionals is essential to the development process (Blandford et al., 2018); hence, some elements of the intervention will be non-dependent on stakeholder views. For example, the addition of physiotherapy videos has been indicated by recent research in paediatric chronic pain (Caes et al., 2018).

Person-Based development is an iterative approach, where qualitative insights are integrated to inform changes to the intervention from the planning stage of development, through to implementation and trialling. Qualitative feedback can be sought using a variety of methodologies, including (however, not limited to) semi-structured interviews, focus groups and think-aloud procedures. For the present study, semi-structured interviews will be used.

The intervention content is based on The Biopsychosocial Approach to paediatric pain management (Liossi & Howard, 2016). This approach emphasises the importance of managing chronic pain using knowledge and techniques from a variety of disciplines, including medicine, nursing, physiotherapy, and psychology. Improving coping skills is a key focus of psychological treatment for paediatric chronic pain (Liossi & Howard, 2016), and is a skill that can be improved using CBT techniques. CBT can also address catastrophizing of pain symptoms in children and adolescents. The research team decided a-priori to include components from each discipline (medicine, nursing, physiotherapy, and psychology) in the intervention, in-line with the biopsychosocial approach.

The intervention will require for the young people and their parents to change their behaviour. A useful theory to consider when addressing long-term changes in behaviour is The Behaviour Change Wheel (Michie, van Stralen & West, 2011). The central element to this framework is a behaviour system (COM-B, which highlights three essential conditions for behaviour change: capability, opportunity and motivation. These essential conditions can be fulfilled using nine outlined intervention functions; at least three of these functions (training, educating, and enabling) can be addressed using the interdisciplinary intervention the current study seeks to develop. Providing an accessible online intervention to adolescents with chronic pain can help to train, educate and enable young people to manage their pain more effectively. Overarching this, the implementation of this type of this intervention in the NHS represents a public service provision, and secures the intervention as an established support service that can facilitate positive behaviour change in the wider population of adolescents with chronic pain, rather than patients attending individual specialist services.

4 RESEARCH QUESTION/ AIM(S)

4.1 Objectives

The current study aims to gain an overall insight as to what adolescents and their parents want to be included in an intervention for paediatric chronic pain.

The primary research question is:

What content and features do young people with chronic pain, and their parents, want to see in an online pain management intervention?

4.2 Outcome

This research aims to identify a set of themes and sub-themes regarding aspects of intervention content and usability using a thematic analytic approach (Braun & Clarke, 2006). Extracted themes will be used to inform the design and content of an online interdisciplinary intervention for paediatric pain management, which will then be re-evaluated in a follow-up study.

5 STUDY DESIGN AND METHODS

5.1 Methodology

Semi-structured interviews (one per participant) will be used to find out what content and features adolescents and parents believe should be included in an online interdisciplinary intervention. The interviewing researcher will agree a mutual time and location with parents.

Informed consent, and assent for minors, will be sought upon recruitment by the research or clinician who recruited the participant, as well as immediately before study participation by interviewing researchers Miss A. Hurley-Wallace (AHW) and Dr D. Schoth (DS).

Age-tailored study information sheets will be provided for adolescents and parents when they are invited to the study (if invited in-person at Great Ormond Street) or when they contact the research team to ask to enrol in the study (if recruited via advertising/ social media). Participant information sheets will be provided again in-person immediately prior to the interview. The parents or guardians of all participating adolescents will be provided with a consent form to sign to indicate that they agree to participate in the study, with the addition of an assent (indication of willingness to participate from a minor) from the adolescents. For the parent participant group, appropriate study information sheets will be provided, and participants will then be given a consent form to sign.

A pre-piloted interview schedule has been developed to guide the conversation. The style of the interview is semi-structured; hence, questions may be asked in any order, and appropriate prompts may be used. All questions in the interview schedule are open-ended e.g. 'what do you think about adding videos to the intervention?' and are worded appropriately for respective ages of participants. The researcher may provide some diagrams of content from other online interventions to prompt the participant. The research may also use generic prompts such as 'Can you tell me a bit more about that?' Interviews are not expected to last longer than one hour. At the end of the interview participants will be debriefed verbally and provided with a debrief form for their records.

One of the researchers (AHW or DS) will be conducting the interviews, face-to-face where possible, which will be audio-recorded for later write-up (transcription) and analysis. Parents may be present during adolescent interviews if they wish, however adolescents aged 12 to 15 may alternatively request a chaperone, which can be provided as long as the interview is not taking place at the participant's home. A researcher may also conduct some interviews with parents, and adolescents aged 16 years + over the telephone.

At the end of the semi-structured interview, participants will also be presented with a 'consent to contact form' and study information for a follow-up study, which will be in the format of a think-aloud interview. Providing consent to contact for the think-aloud study is not compulsory.

5.1.1 Follow-up study – approvals

The Clinical Research Adoptions Committee (CRAC) (GOSH) strongly recommended that the participants in our study would be well placed to evaluate the final intervention. See section 8.3 for full statement of rationale for including think-aloud interviews as part of this application. NHS Research Ethics Committee (REC), Hampshire 'B', have requested that the online content to be used for the follow-up study must be submitted via IRAS, to the REC as a substantial amendment for review. Participants will not be approached to participate in the follow-up study until the content material has been reviewed and approved by the REC.

5.1.2 Follow-up study - procedure

Think-aloud interviews are a qualitative methodology, within which participants are presented with the draft intervention content and asked to say aloud their thoughts about the content (as well as other aspects they wish to comment on) as they navigate through the intervention. Think-aloud techniques have been cited as a useful method for conducting usability studies in children (Donker & Markopoulos, 2002). The procedure used in this study will be similar to that described by Boren and Ramey (2000), which is recommended for usability and feasibility type studies (Krahmer & Ummelen, 2004). This approach allows for flexible prompts, unlike traditional approaches to the think-aloud method, which advise to only use "keep on talking" (Ericsson & Simon, 1993). Using the approach by Boren and Ramey (2000) researchers can provide acknowledging utterances throughout the process, using prompts such as "And now..." which are thought to be less likely to interrupt free-thinking and illicit apologies from the participants.

Each participant will undergo one think-aloud interview, hence all participants have the opportunity to participate in a maximum of two interviews (the semi-structured interview and the think-aloud). The intervention content to be presented to participants will be in a modular format on a computer. Participants will be asked to say aloud their thoughts whilst they are working through the content. All utterances will be audio-recorded. A practice task will also be conducted, to help participants get used to talking aloud. The procedure should not take more than 1 hour. At the end of the task, participants will be debriefed verbally and provided with a debrief form for their records.

The content will include modules that present multi-modal chronic pain management techniques. All content will be informed by healthcare professional input, as well as by the Royal College of Paediatrics in Child Health (RCPCH) e-learning Pain Management course, which was developed as a pain education tool for professionals using a biopsychosocial, interdisciplinary perspective (Hurley-Wallace, Wood, Franck, Howard & Liossi, 2018). Adolescent and parental insights gathered from the first set of interviews will be integrated into the content and design of the intervention where possible; however, the basic modules that are to be included will cover the following areas in line with clinical practice in the UK:

- Pain education;
- Medications;
- SMART goals/ goal-setting;

- Physiotherapy;
- Non-pharmacological physical therapies e.g. using a TENS machine (NHS, 2019);
- Multi-component CBT e.g. relaxation, breathing, mindfulness;
- Sleep hygiene;
- School support and daily activities;
- Transitional care.

Pain education will be the first module presented to all participants, and transitional care will be the last module presented to all participants. The final order of the other modules is not yet defined, and is likely to be a flexible order.

The draft content that will be shown to participants will be uploaded to the IRAS checklist for this study, for review by the REC, before any participants are recruited for the follow up study.

5.2 Analysis

All data from semi-structured and think-aloud interviews will be analysed thematically (two separate analyses). The current study intends to abide by the six phases of thematic analysis, as outlined by Braun and Clarke (2006). The first stage phase includes familiarizing yourself with the data: transcribing audio data, reading, and re-reading. The second phase is code generation, which involves systematically coding interesting features of the data that are noticed across the data set. The third phase is searching for themes. To do this, codes are grouped together to form potential themes; Braun and Clarke (2006) describe a theme as follows: *“A theme captures something important about the data in relation to the research question, and represents some level of patterned response or meaning within the data set.”*

The fourth phase involves reviewing themes and checking if they fit the initial coded extracts, as well as whether they fit the entire data set. At this stage, a thematic map of the analysis can be created – this is similar to a spider diagram or mind map. In the fifth phase, the aim is to define the specifics and finalise the names of extracted themes. The sixth and final phase is the production of the report. A selection of compelling quotes from the data can be included in the report to provide an example of each theme. Selected extracts from the data may be analysed further for the purpose of the report, and the analysis will be related back to the research question and wider literature.

All utterances made by participants during the interview procedure will be transcribed and coded individually by AHW using NVivo qualitative analytic software. Coded data will be organised into a variety of themes and sub-themes representative of participant views on intervention content and features; this will be done by AHW. Sections of the transcripts will be sent to Prof. C. Liossi or DS to be coded using the developed themes/ sub-themes (back-coded), and inter-rater reliability will be assessed using the Kappa statistic. Any disagreements regarding themes will be resolved through discussion with the research team. Finalised themes and insights will then be used to inform changes to the intervention; this will be an iterative process, where the semi-structured interviews will inform the

first round of changes to the intervention, and the think-aloud interviews will inform a second round of changes.

The analysis for this study will use a constructivist epistemological approach; a naturalistic enquiry method, which considers that the surrounding environment and context has an impact on how individual's attribute meaning, such that each individual forms their own version of reality (Lincoln & Guba, 1985). This study will also adhere to the 15-point checklist of criteria outlined for good thematic analysis (Braun & Clarke, 2006), which covers the transcription, coding, analysis, overall quality, and final report.

6 STUDY SETTING

The current study is a multicentre study. Participants will be identified by collaborating clinicians at GOSH and RMH; clinicians will then advise AHW of which patients are happy to be approached, and AHW will invite potential participants with the study information sheet and contact details should they wish to participate. This will be done in person at the site in question as much as possible. At GOSH, some participants may also be recruited by letter or email by clinicians Prof. C. Liossi (CL) and Miss S. Lilley (SL). Participants may also be recruited in this way at RMH by Dr AK Anderson. Additional participants will be recruited from social media, the wider community and charities, or patient organisations (see section 7.3.1).

Interviews will be conducted in private rooms at either one of the specified hospital sites or at the Pain Research Laboratory at the University of Southampton, Psychology building where possible. This setting will allow the researchers to control for excess noise or distractions. Participants also have the opportunity to request home interviews if they wish. In these instances, the researcher attending the participant's home will abide by the University of Southampton Lone Working Policy (March 2017). Researcher AHW has attended University of Southampton Training in Personal Safety for Lone Working. This policy is included as a supplement to this protocol.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

Eligible adolescent participants will be a) aged 12 to 17 years, b) been experiencing chronic pain (cancer or non-cancer related) that has lasted for at least three months (Treede et al., 2015), and c) patients in the cancer related pain group must not have received treatment to eradicate cancer in the last three months; biological and pharmacological maintenance therapies are acceptable.

Eligible parent participants will be a) parents or legal guardians of adolescents (aged 12 to 17 years, experiencing chronic pain of any type).

7.1.2 Exclusion criteria

The current study will exclude adolescents who a) cannot communicate in fluent, spoken English*, b) are aged 18 or over, and c) for the cancer pain group are continuing to undergo treatments to eradicate their primary cancer or have received these treatments in the last three months.

The current study will exclude parents who a) do not speak fluent English*

*The research team does not have any translators, and poor English skills may lead to language misinterpretation in the qualitative analysis to follow.

7.2 Sampling

7.2.1 Size of sample

The overall sample size projected is a group of 60 stakeholders (teenagers and parents).

The study aims to recruit approximately 15 participants per group at GOSH:

- Children with chronic pain (n = 15)
- Parents of children with chronic pain (n = 15),

Approximately 10 participants per group will be recruited from RMH:

- Children with cancer-related chronic pain (n = 10)
- Parents of children with cancer-related chronic pain (n = 10),

Approximately 5 participants per group will be recruited from the community:

- Children with chronic pain (any type) (n = 5)
- Parents of children with chronic pain (n = 5)

Analysis will be ongoing and recruitment will continue up until the point of saturation (Guest et al., 2016). The research team anticipate that approximately 15 participants per group will be sufficient for saturation, as has been the case in similar intervention development studies conducted in the field of paediatric pain management (e.g. Stinson et al., 2014). We hence aim to recruit this baseline amount of 30 participants at GOSH (15 parents and 15 children), with the addition of insights from community volunteers, as well as children and parents from the Chronic Cancer Pain Clinic at RMH.

7.2.2 Sample diversity

As we are using an opportunistic sample the research team cannot guarantee complete representation across sexes, pain diagnoses, chronicities, or otherwise. If the sample is misrepresentative in any way, this will be accounted for in the qualitative analyses and discussed in the study write-up. Participants may be from either a clinical or a non-clinical population; there is no guarantee of whether a higher proportion of the sample will be recruited from Great Ormond Street Hospital versus the wider community.

A representative sample would include a mixture of ages ranging from 12 to 17 years, and a representative split between the sexes (chronic pain is more common in teenage girls compared to boys). A fully representative sample would also include a mixture of adolescents from varying socio-economic backgrounds. Adolescents are likely to have a variation of pain diagnoses and chronicities, however if this is not the case then this will be discussed in the study write-up.

Similarly, for the parent feedback groups, a representative sample would include parents of children with a mixture of chronic pain diagnoses, a mixed sample of mothers and fathers, and parents from a variety of socio-economic backgrounds.

7.2.3 Sampling technique

Adolescent participants and their parents will be primarily sampled from GOSH Pain Control Service. If recruitment is successful, the secondary hospital collaboration will be implemented, and participants will additionally be sampled from RMH Chronic Cancer Pain Clinic. Where possible, opportunity sampling will be used to find additional adolescent and parent participants from the community, voluntary services, social media, and patient organisations.

A local newspaper advertisement will be circulated (online and paper format) to advertise the study. Participants will also be sought using poster advertisements (online and paper format). This includes advertising the study using posters at the specified NHS sites where possible. Approval from a collaborating clinician at each site will be sought prior to advertisement at the site in question. Copies of the study poster advertisement and newspaper advertisement are available as a supplement to this protocol. This variety of sampling techniques widens participation and provides the opportunity for any paediatric chronic pain patients or parents to contribute to the study if they would like to.

The research team will be recruiting participants from GOSH and RMH for up to one year, however recruitment from the community will continue for an additional 8 months, hence the total study duration is 1 year 8 months.

7.3 Recruitment

7.3.1 Sample identification

Participants recruited from NHS hospitals will primarily be identified by co-applicants who are part of the patient's clinical care team at the site in question. Participants will be identified by collaborating clinicians or the PI; clinicians will then advise AHW of which patients are happy to be approached. AHW will then invite potential participants to the study in-person at the pain clinic, by providing the participant information sheet and researcher contact details should they wish to participate. Participants will then be given time to think about whether they would like to join the study and may contact the central research team to enrol formally at a later date. Recruitment will be conducted in this way as much as possible. At GOSH, some participants may also be recruited by letter or email by clinicians CL and SL. Participants may also be recruited in this way at RMH by Dr AK Anderson.

AHW will additionally identify other potential adolescent and parent participants by searching social media for groups that meet eligibility criteria, for example a forum for parents of children with chronic pain. Voluntary services in London and Southampton will be investigated to see if any groups may match the eligibility criteria. If so, the admin or the lead of the group will be approached to ask if they can advertise the study, or alternatively to ask permission for the research team to advertise the study within the group or organisation. Study advertisement materials (poster and newspaper advertisements) provide the contact details of the research team, so that potential participants can contact AHW or CL if they would like to take part.

All participants will be offered travel expenses. These funds will be taken from the research expenses that are part of University of Southampton funded studentship for AHW. For adolescents, all and any reimbursements will be made to the consenting parents or guardians.

Participants that take part in the semi-structured interviews will be given the option for the research team to retain their contact details, so that we may contact them about taking part in the think-aloud study. Hence, some participants may be re-recruited following approval of the content for the follow-up study. In addition, the same community recruitment strategy will be used as described for the semi-structured interviews, however new advertisements will be uploaded for approval by the REC as part of the substantial amendment required for the think-aloud study.

7.3.2 Consent

Consent is an ongoing process. AHW will initially invite potential participants to the study in-person at the pain clinic, by providing the participant information sheet and researcher contact details should they wish to participate. Participants will have time to think about whether they would like to participate and will be formally enrolled to the study at a later date. Informed consent, and assent for minors, will additionally be sought immediately before study participation by interviewing researchers AHW and DS.

Prior to the start of the interview, all participants and/or their legal representative will be presented with an information sheet detailing the procedure of the study, their right to withdraw consent at any time, and the dissemination of results. Separate information sheets, which are age appropriate for adolescents, will be provided. This information will be reiterated by AHW or DS. Participants will be given the opportunity to ask any questions they may have, before being presented with a consent/ assent form. The forms are worded in an age-appropriate manner for all participants. No activities designed for this study will begin before informed consent is received.

Any participants under the age of 16 years will be asked to assent with the addition of informed consent sought from the parent or guardian. Informed consent from the parent or guardian is compulsory for minors, hence adolescents will not be allowed to participate without parental/ guardian consent. Consent without assent will also not be accepted, and as such, the adolescent in question would not be allowed to participate.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

8.1.1 Safeguarding of children and teenagers

The research team is responsible for the safeguarding of children and teenagers taking part in this study. If a member of the research team has reason to suspect physical, emotional or sexual abuse, or neglect, normal escalation procedures will be followed and the most appropriate person will be informed. This preceding statement is included on all version of the participant information sheet.

The research team are aware that safeguarding issues could arise during any form of patient contact. For participants recruited from participating hospital sites, if abuse or neglect is suspected the safeguarding officer for that hospital will be contacted, such that the safeguarding process can be carried out in-line with hospital standards. For participants recruited from the community, social services will be informed. In the case of suspected immediate danger to a child or teenager, the police will be contacted via emergency services; a member of the research team will remain with the young person whilst the police are contacted. Any safeguarding issues that arise will be prioritised and dealt with efficiently, without causing alarm to the young person in question as much as possible.

8.1.2 Protection of participants from psychological harm

The research team do not anticipate there to be any distress or disadvantages due to taking part in this study. It is possible that some interview questions, or some content that we display to the participants, could provoke stressful thoughts about the adolescents' chronic pain condition. As researchers, we are aware of this and would stop the interview or task to check that the adolescent or parent participant is happy to continue with the study if they appeared to be becoming distressed. We will stop the study if the participant becomes noticeably upset or emotionally/ psychologically distressed.

In the case of any emotional or psychological distress, trained clinicians will be on hand to help deal with this immediately. This includes clinical nurse specialists at GOSH and Psychologist CL at the University of Southampton. If the interview is taking place at a participant's home – AHW will contact CL for assistance.

We do not expect anticipate any long-term distress will be caused by participating in the study. Any cases of long-term distress will be advised to contact the research team, so that we may refer them to the most appropriate person/ team.

8.1.3 Chaperones

Parents/ guardians may be present with adolescents under 16 years during the study if they wish, however, the adolescent must agree for them to be present. If there is any disagreement between the two parties, the adolescent and parent in question will be advised that they can no longer take part in the study.

Adolescents may not wish for their parent/ guardian to be present and may ask for someone else to accompany him or her instead. We can provide a chaperone to accompany them if they wish, however this cannot be done for home interviews. Researchers must consider safeguarding implications with regard to chaperone requests.

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

Before the start of the study, approval will be sought from the UK Health Departments Research Ethics Service (NHS REC), with the addition of a governance review from the University of Southampton for the study protocol, study information sheets, consent forms and other relevant documents.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement changes at the site. All correspondence with the REC will be retained by the research team.

The Chief Investigator will produce the annual reports as required by the REC and will notify the REC of 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. Within one year after the end of the study, the Chief Investigator CL will submit a final report with the results, including any publications or abstracts, to the REC.

In the instance that the study is ended prematurely, the Chief Investigator will notify the REC, and provide reasons for the premature termination.

Regulatory Review & Compliance

Before GOSH or RMH enrolls patients into the study, the Chief Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Approvals from participating organisations (GOSH and RMH) will be in place prior to the start of the research. This project will be registered with GOSH using the guidance as advised for unfunded projects, which is available at: <https://www.gosh.nhs.uk/research-and-innovation/information-researchers/joint-rd-office/registering-project-or-funding-application#Unfunded>

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D at GOSH and RMH sites, as well as the study delivery team) so necessary arrangements can be put in place to implement the amendment(s) and confirm their support for the study amendment(s).

Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

The Chief Investigator is responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial. Substantial amendments must be completed via IRAS and validated by the REC that approved the original application. Any non-substantial amendments can be emailed to hra.amendments@nhs.net, using the template available at <https://www.hra.nhs.uk/approvals-amendments/amending-approval/>.

Guidance on the categorisation of amendments for studies involving the NHS can be found on the HRA website. <http://www.hra.nhs.uk/resources/after-you-apply/amendments/>. Any amendment made to the research protocol will be documented by updating the version number.

8.3 Peer review

The research team has reviewed this research protocol.

This protocol has been reviewed and accepted by the Clinical Research Adoptions Committee (CRAC) at Great Ormond Street Hospital.

The CRAC strongly recommended that the participants in our study would be well placed to evaluate the final intervention. As informed by patient representatives within the CRAC, the research team have developed a single application for this project based on recruitment, development and testing of the online resource, which presents minimal risk to the patients or participants. This protocol, and the IRAS Ethics application, hence include consent to contact participants for the second part of the study, which will be a think-aloud study (described in section 5.1). This follow-up study will not start recruiting participants until the content that we are showing participants has been submitted to the REC, and approved as a substantial amendment.

8.4 Patient & Public Involvement

Patients and carers will be participating in the research. The study will involve interviewing a mixture of patients, and parents or guardians of patients recruited from GOSH, RMH and the wider community. Insights from the qualitative study will inform alterations to the online intervention as part of an iterative process.

We will also ask participants over the age of 16 years if they would like to join the design team.

Patients, carers, and members of the public will not be involved in the management or design of the research, the analysis of results or dissemination of findings. These aspects will be managed by the research team and collaborating clinicians.

8.5 Protocol compliance

In the instance that the research protocol is deviated from, changes or errors will be reported to the Chief Investigator. Any changes will be documented on a new version of the protocol and published accordingly.

Frequent deviations from protocol are unacceptable and may require immediate action. The Chief Investigator will determine how to proceed in this case.

8.6 Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Participants will be allocated a pseudonym that does not contain any personal information. For example, participant 'Joan Smith' may be given a pseudonym data label such as 'Starling1'. Participants from the same family will be grouped by pseudonym such as 'Robin1' and 'Robin2'. Pseudonyms will be kept in a password protected data key file that only the central research team will have access to (AHW, LJ, DS and CL). Each participant's data will be labelled with their pseudonym, so that data remains anonymous, however, if they later wish to withdraw their data, this may be done using the data key file.

For the purposes of patient note keeping, consent forms will remain to have participant names and signatures on them. Paper copies of consent forms will be stored in a securely locked file within offices in the University of Southampton Psychology Department building.

Participants will not be able to withdraw their data once their interview has been transcribed. This will be made clear in the study information sheet. The study information sheet for participating parents and consenting parents will also include the University of Southampton Data Protection Privacy Notice.

All data stored electronically will be subject to a process of direct de-identification through pseudonymisation to ensure confidentiality; only the researchers listed on this protocol will have access to the final study dataset (see section 8.8), and all files will be password protected. All identifying information obtained during interviews will be removed and replaced with an appropriate pseudonym, for example, the name of a school may be taken out and replaced with a fictional name.

Paper copies of consent forms, and any other personal or sensitive data will be stored securely in a locked file in offices within the University of Southampton Psychology Department building. Following study completion and publication, all sensitive or personal data will be destroyed. The data custodian for this project is the principal investigator, Professor C. Liossi.

8.7 Indemnity

1. Regarding legal liability of the sponsor for harm to participants arising from the management or design of the research:

The University of Southampton (sponsor) has insurance in place for Errors and Omissions to indemnify the insured in respect of claims first made against the insured during the period of the policy arising out of negligent acts, errors or omissions.

2. Regarding the legal liability of investigators or collaborators (GOSH and RMH clinicians) arising from harm to participants in the conduct of the research:

NHS indemnity scheme or professional indemnity will apply (participants NHS sites only).

University of Southampton insurance may also apply where the cause of the harm was not due to clinical negligence as covered by CNST.

3. Payment of compensation, by the sponsor, in the event of harm to the participants where no legal liability arises is not applicable; the study is qualitative using semi-structured interviews only.
4. No equipment is provided to the sites for the purpose of the study; hence, no arrangements for insurance or indemnity in relation to the equipment (e.g. loss, damage, or harm to participants or site staff) are applicable.

8.8 Access to the final study dataset

Study information sheets will outline how study data will be used in the context of the wider research project (online intervention development). This will be worded in an age-appropriate manner for adolescents.

Only members of the research team conducting interviews and conducting or overseeing analyses (central research team) will have access to the full data set:

- Miss Anna Hurley-Wallace,
- Miss Lauren Johnstone,
- Prof. Christina Liossi,
- Dr Daniel Schoth

Personal data will only be used by the research team to arrange face-to-face interviews, and to conduct interviews by telephone. Personal details of participants may also be used to identify anonymised data in the case that a participant wishes to withdraw their data from the study.

Dr Glyn Williams, Miss Suzanne Lilley and Dr Anna Karenia Anderson will only have access to data relating to their own patients.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The University of Southampton owns the data arising from this study. On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared. This research will be presented at the participating centres GOSH and RMH (monthly meetings of clinicians), and will be written up for publication in a peer-reviewed journal. Study methodology and results will be reported in AHW's PhD thesis.

GOSH and RMH collaborators will be acknowledged in any publications resulting from this study.

All adult participants and parents/ guardians of participating children will be asked if they would like to be notified about the outcomes of the study at the end of the interview. If they would like to be notified, this would take place after the Final Study Report has been compiled - they will be sent the report with a cover letter lay summary. Participants may also request results from the Chief Investigator or AHW after the Final Study Report had been compiled. Details of who to contact for

further information about the study are provided in the study information sheet and debrief form (adult and parent/ guardian versions).

The study protocol and full study report will not be made publically available.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The research team will all be eligible authors for any publications resulting from this work:

- Miss Anna Hurley-Wallace,
- Miss Lauren Johnstone,
- Prof. Christina Liossi,
- Dr Daniel Schoth
- Dr Glyn Williams,
- Miss Suzanne Lilley,
- Dr Anna Karenia Anderson

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11 APPENDICES

11.1 Appendix 1- Required documentation

The following documentation is required prior to initiating research at GOSH and RMH sites:

- Qualitative research protocol (current form) (HRA headed paper)
- Participant Information Sheets – Adolescents*
- Assent forms – Adolescents*
- Participant Information Sheets – Consenting Parent/ Guardian*
- Consent forms – Consenting Parent/ Guardian*
- Participant Information Sheets – Parents and adults aged 16+*
- Consent forms – Parents and adults aged 16+ *
- Debriefs for Adolescents (Under 16's)*
- Debriefs for Adults*
- Consent-to-contact consent form – Consenting Parent/ Guardian*
- Consent-to-contact consent form – Participating Parents*
- Interview Schedule (optimised for adolescents and parents)
- Study poster advertisement
- Study advertisement for local newspaper
- Statement of activities
- Schedule of events
- Clinical Research Adoptions Committee (CRAC) approval documentation
- University of Southampton Lone Working Policy

*participant information sheets, consent and debrief forms, and advertisement should be on University of Southampton headed paper.

11.2 Appendix 2- Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	04/01/2019	Anna Hurley-Wallace	<p>Protocol number and dates adjusted to match within document and headers/ footers.</p> <p>Addition to section 7.3.1. "Approval from a collaborating clinician at each site will be sought prior to</p>

				advertisement at the site in question.” Required documentation – statement of activities and schedule of events added.
2	1.2	29/01/2019	Anna Hurley-Wallace	Researcher Dr Daniel Schoth added as interviewing researcher additional to Miss A. Hurley-Wallace. Several small changes made to GOSH processes in-line with changes made to the CRAC application form.
3	1.3	05/02/2019	Anna Hurley-Wallace	Edits to pseudonymisation process with advice from University of Southampton research governance – section 8.6. Edits to dissemination policy 9.1 from participants will not be notified of outcomes to “All adult participants and parents/ guardians of participating children will be asked if they would like to be notified about the outcomes of the study at the end of the interview.”
4	1.4	24/03/2019	Anna Hurley-Wallace	Suggested amendments added in-line with CRAC review (GOSH): <ul style="list-style-type: none"> - Sample age range adjusted to 12 to 17 years. See section 7. Sample diversity clarified in section 7.2.2. - Added consent to contact for second (follow-up) study, and methodology details of follow up study (think-aloud). See section 5.1.1. Reasoning for this added to peer review statement, section 8.3. - Necessary adjustments to Gantt chart to incorporate changes. See study flow chart
5	1.5	12/06/2019	Anna Hurley-Wallace	Amendments added to comply with requests from REC Hampshire B: <ul style="list-style-type: none"> - Children with statement of special needs to be included in the study – eligibility section 7.1 - Sample diversity statement altered - Social media recruitment clarified

				<p>(7.3.1.)</p> <ul style="list-style-type: none">- Updated information on safeguarding and chaperones added to section 8.- Removed all mentions of letter to GP
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