Mechanisms Of Change in Adolescent Pain Self-management (MOCAS)

Unique Protocol Identification Number:
National Clinical Trial (NCT) Identified Number: NCT04043962
Principal Investigator: Tonya Palermo
Sponsor: Seattle Children's Research Institute

Grant Title: Role of sleep deficiency in self-management of pediatric chronic pain
Grant Number: R21NR017312
Funded by: NINR
Version Number: v.0.025
2 November 2018

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Investigator's Signature

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 11-02-2017

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1 PROTOCOL SUMMARY

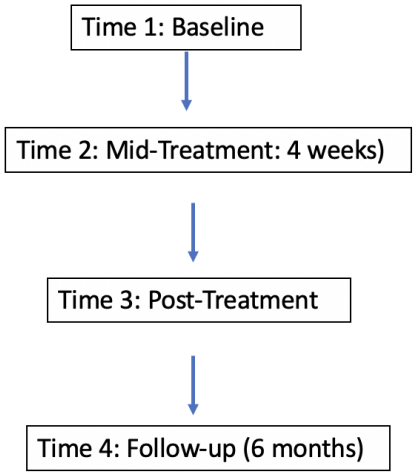
1.1 Synopsis

Title:	Mechanisms Of Change in Adolescent Pain Self-management (MOCAS)	
Grant Number:	R21NR017312	
Study Description:		
Objectives*:	Primary Objective:	The study objective is to characterize how sleep deficiency influences youth's ability to engage with, implement, and benefit from pain self-management intervention.
	Secondary Objectives:	
Endpoints*:	Primary Endpoint:	6 months
	Secondary Endpoints:	Immediate post-treatment (10 weeks)
Study Population:	The study population includes 80 youth with chronic musculoskeletal, head, or abdominal pain (pain for longer than 3 months) who are ages 12-17 years. Both males and females will be included. All youth will have received an evaluation for complex chronic pain in the Seattle Children's Pain Clinic.	
Phase* or Stage:	Phase 1	
Description of Sites/Facilities Enrolling Participants:	The study site is Seattle Children's Hospital. No sites outside of the United States will be included	
Description of Study Intervention/Experimental Manipulation:	The study intervention is a pain self-management intervention called WebMAP (Web-based management of adolescent pain) delivered via the internet. The length of the intervention is 8 weeks and youth and parents complete one 15-minute module per week. The eight child modules include: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) deep breathing and relaxation, 4) implementing coping skills at school, 5) cognitive skills (e.g., reducing negative thoughts), 6) lifestyle interventions, 7) staying active (e.g., pleasant activity scheduling), 8) relapse prevention. The eight parent modules are: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) operant strategies I (using attention and praise to increase coping), 4) operant strategies II (using rewards to increase positive coping and reach school goals), 5) modeling, 6) lifestyle, 7) communication, 8) relapse prevention.	
Study Duration*:	The duration of the study is 24 months.	

Participant Duration: Participant duration is 6 months.

1.2 Schema

Study Flow



1.3 Schedule of Activities

	Pre-Screening	Consent	Time 1	Time 2	Time 3	Time 4
EMR Review Eligibility	X					
Informed Consent		X				
Demographics			X			
Sleep assessment			X		X	X
Outcome evaluation			X		X	X
Mediator evaluation				X		
Intervention			X	X		
Adverse events reporting				X	X	X

2 INTRODUCTION

2.1 Study Rationale

Five to 8% of youth report severe chronic pain and disability. Pediatric chronic pain is costly to society, with estimates of $19.5 billion/year spent in the US on direct healthcare costs. History of childhood chronic pain places youth at risk for a lifelong pattern of pain, disability and high health care costs in adulthood. Thus, finding effective methods that support youth in pain self-management is a priority. Our preliminary data suggest that youth with greater sleep deficiency find pain self-management intervention less acceptable and make fewer gains in pain-related outcomes, indicating that sleep may represent an overlooked health factor affecting self-management skills. Although progress has been made in establishing pain self-management interventions for youth, treatments produce wide variability in patient response and do not target sleep deficiency.

Therefore, the objective of this application is to characterize how sleep deficiency influences youth's ability to engage with, implement, and benefit from a pain self-management intervention. We will study a cohort of 80 youth receiving internet-delivered pain self-management over an 8-week period. Sleep deficiency will be comprehensively assessed with subjective measures, daily sleep logs, and ambulatory actigraphy monitoring to measure disrupted sleep, amount of sleep, sleep quality, and insomnia symptoms. Following the recommended Common Data Elements for self-management we measure three self-management processes including patient activation, pain self-efficacy, and self-management skills, and assess patient-reported treatment engagement and health (global health, fatigue) and pain outcomes (pain symptoms, pain-related disability). Positive and negative affect and executive functioning will be assessed as potential mediators. The next steps in this research program are to enhance the effectiveness of pain self-management interventions by addressing co-occurring sleep deficiency. Specific aims and hypotheses are:

Aim 1. Characterize the relationship between baseline sleep deficiency and self-management processes. H1. Greater baseline sleep deficiency (shorter sleep duration, poorer sleep quality, increased insomnia symptoms, greater wake time after sleep onset) will be associated with lower activation, lower pain self-efficacy, and lower use of self-management skills from pre- to post-treatment. H2. Positive and negative affect and executive functioning will mediate the relationship between sleep deficiency and self-management processes.

Aim 2. Determine the effect of baseline sleep deficiency on treatment acceptability, engagement, and benefit from an internet-delivered pain self-management intervention. H3. Greater sleep deficiency will be associated with lower perceptions of treatment acceptability and engagement (fewer logins, fewer completed treatment modules and assignments). H4. Greater sleep deficiency will be associated with less benefit (fewer improvements) in ratings of global health, fatigue, pain symptoms, and pain-related disability following pain self-management intervention. H5. Positive and negative affect and executive functioning will mediate the relationship between sleep deficiency and treatment acceptability, engagement and benefit.

2.2 Background

Chronic Pain and Sleep Deficiency. Pain that persists for longer than three months is common; 5-8% of youth report severe and disabling chronic pain (1). These youth demonstrate elevated anxiety and depressive symptoms as well as difficulty attending school, participating in sports and physical activities, and maintaining social participation (2). Sleep deficiency is defined as a deficit in the quantity or quality of sleep obtained versus the amount needed for optimal health, performance and well-being (3). Sleep deficiency is highly co-morbid, affecting over half of youth with chronic pain (4, 5). Sleep deficiency is associated with diminished physical function, poorer quality of life, and increased anxiety and depressive symptoms (6, 7). Sleep problems comorbid with chronic pain are also recognized as costly in terms of prescription medications, health care use, and lost work productivity (8, 9), compounding the negative financial toll of chronic pain.

The interrelationship between sleep deficiency and pain. Early models described a bidirectional relationship between pain and sleep (10), where uncontrolled pain can cause sleep disruptions, and in turn, disturbed sleep can enhance pain sensitivity (11). Recent research has demonstrated that more studies now support the direction of sleep impacting pain than vice versa. That is, sleep deficiency has now been shown to lead to subsequent increased pain. Findings are from studies using experimental and self-report designs in multiple samples across childhood and adulthood (12), highlighting its relevance in chronic pain treatment.

Self-Management Interventions for Pediatric Chronic Pain. There are compelling longitudinal data demonstrating that childhood chronic pain places individuals at significant risk for developing or continuing with chronic pain into adulthood (13). Thus, learning effective pain self-management in childhood may be critical for preventing or lessening the enormous economic and societal impact of adult chronic pain. Self-management interventions including cognitive-behavioral therapy (CBT) offer safe and effective alternatives to medications for chronic pain and progress has been made toward developing effective self-management pain interventions for children. *Our own internet-delivered pain self-management program (WebMAP) has shown efficacy in reducing children's pain-related disability, anxiety, and depressive symptoms (14). However, treatment produces small to moderate effect sizes and there is wide variability in treatment response.* To date, very little research has been conducted on moderators or mediators of treatment benefit, and no consistent variables have been identified. Thus there is limited empirical understanding of how to enhance the effectiveness of pain self-management interventions for children.

Conceptual Model of the Effect of Sleep Deficiency on Pain Self-Management. While conceptualizations of self-management vary, the construct generally refers to the daily activities that individuals must perform to keep their illness under control, minimize its impact on their physical health and functioning, and cope with any comorbid or resulting psychological symptoms (15, 16). Successful self-management in youth involves fostering patient and family self-efficacy and motivation for making behavioral changes.

We propose that sleep deficiency is a modifiable pathway that may influence success of pain self-management. Sleep deficiency is associated with general deficits in higher-order and complex cognitive functions and reduced self-regulatory skills (e.g., 17), which may influence self-management tasks. As reviewed by Stickgold and Walker (2013), sleep (a) enhances cognitive flexibility in problem solving (19, 20), (b) assists in the integration of new learned information (21), and (c) is critical for promoting memory associations (22). Sleep also affects elements of self-control such as subjective effort, perceived exertion, and choice (23) and short sleep duration increases negative affect and decreases positive affect (24). *Because self-management relies on organization, memory, and behavioral activation, we hypothesize that positive and negative affect and executive function will mediate the relationship between sleep deficiency and self-management*. Relevant research in other pediatric chronic conditions has examined effects of sleep deficiency on self-management behaviors in youth. For example, in a study in youth with diabetes, greater sleep deficiency was related to reduced treatment adherence (25). Similarly, in youth receiving a physical activity self-management intervention, greater sleep deficiency was related to reduced efforts at self-monitoring, goal-setting, and social support behaviors (26). Thus, our scientific premise is that in addition to the direct effect of sleep on pain and functioning, sleep deficiency also decreases youth's acceptability of treatment, motivation to engage with treatment, and to implement self-management tasks and behaviors.

This scientific premise is supported by our own pilot data showing that several aspects of sleep deficiency are related to treatment acceptability and outcomes. Specifically, in pilot work we found that shorter sleep duration at baseline predicted reduced benefit (i.e., less improvement in pain-related disability) with a self-management
intervention for chronic pain (27) and that poor baseline sleep quality was associated with lower youth perception of overall treatment acceptability. However, to date, studies have not determined the impact of sleep deficiency on pediatric pain self-management.

Use of the Internet to Deliver Pain Self-Management. Even though pain self-management has been shown effective, major barriers exist for families to access this care due to the geographical distance and limited scheduling that prevents most patients from receiving psychological intervention (28). Availability of information and communication technology has expanded opportunities for intervening with families remotely, and internet-delivered chronic pain self-management interventions have been found effective in both adult and pediatric populations (29) for managing pain and disability. We have had tremendous success in our research studies reaching families using Internet and smartphone technologies.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Risks for this study concern the potential for emotional distress, loss of confidentiality, and a burdensome time commitment. Study questionnaires and the websites contain material concerning pain and psychosocial functioning that may elicit emotional discomfort. To mitigate this discomfort, all

aspects of the study are voluntary. We will inform participants that if they feel uncomfortable completing any part of the study, they can let us know and stop participating in that part of the study. Participants will also be informed that their data will be safeguarded to preserve confidentiality. Participants will be instructed to access the programs in a safe place (e.g. not while driving or completing other tasks). Burden related to the length of the questionnaire assessments and lessons will be kept at a minimum, such that parents and adolescents will likely spend about 20-30 minutes completing questionnaires at each time point, and 20-30 minutes for each lesson. Daily assessments take ~2 minutes. Because the data collection system, REDCap, will save and store responses from questionnaires, children and parents may log on and off at their convenience to complete assessments. Due to the fact that we are acquiring information from children and parents online, we are sensitive to the need to carefully safeguard all data entered on the app. Protected health information will not be collected on the app. All study data will be safeguarded using secure password-protected servers at Seattle Children's Hospital. The primary source of data will come from questionnaires, which will be collected in an encrypted manner and stored in secure password-protected databases. All contact information from the referrals will be stored in a secure database within the PIs' research lab at Seattle Children's Research Institute (SCRI). The participant codebook will be kept on a password protected server to which only study staff has access.

2.3.2 Known Potential Benefits

Participation in this research may or may not benefit the participant. Completion of the CBT program delivered via the website may help to reduce pain and improve functioning in adolescents. Information collected will provide useful data regarding how sleep influences response to psychosocial treatment for chronic pain in adolescents that may inform implementation of effective treatments for adolescents with pain. After the study is completed and results are published, we will send participants an email about what we learned.

2.3.3 Assessment of Potential Risks and Benefits

The potential risks of participation to the participants are considered to be minimal in relation to the potential gain in critical knowledge of how sleep influences the benefits from psychosocial intervention to improve pain outcomes in youth.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	TIMEFRAME
Characterize the relationship between baseline sleep deficiency and self-management processes.	The Pain Self-Efficacy Scale (45) is a 7-item measure that assesses the child's beliefs in carrying out activities when in pain. The scale has demonstrated good internal consistency, cross-informant reliability with parent report, and strong construct validity.	T1, T3, T4
	The Patient Activation Measure (46) is a 13-item questionnaire that assesses an individual´s knowledge, skill and confidence for managing their health and health care. The PAM uses a 0-100 scale resulting in 4 levels of activation, from low (1) to high (4). The measure is not disease specific, and has been successfully used with a wide variety of chronic conditions. Although developed for adults, the PAM has been used in children ages 12 and above, is reliable, and shows strong construct validity. Self-management skills.	T1, T3, T4
Determine the effect of baseline sleep deficiency on treatment acceptability, engagement, and benefit from an internet-delivered pain self-management intervention.	Pain intensity will be measured using the 11-point NRS (numerical rating scale) completed by children via daily diary assessments over a 7-day period. Scores are averaged at each timeframe with higher scores indicating higher pain intensity.	T1, T3, T4
	The Child Activity Limitations Interview (CALI-9) is a daily diary validated to assess perceived difficulty in completing 9 daily activities as a measure of pain-related disability. Responses are rated on a 5-point scale (0-4) with higher scores indicating greater perceived difficulty with activities. Youth will provide ratings daily for 7 days on their online diaries at each assessment period. Mean total activity limitations across the reporting period is used in analyses, with higher scores indicating greater disability.	T1, T3, T4

4 STUDY DESIGN

4.1 Overall Design

This is a single arm trial to identify mechanisms of response to CBT intervention. All youth will receive active intervention, the Web-based Management of Adolescent Pain intervention.

4.2 Scientific Rationale for Study Design

Prior randomized controlled clinical trials have already established efficacy of this intervention approach. Our aim is not to examine efficacy of pain self-management, but rather to identify the role of sleep deficiency on self-management behaviors, and our pre-post design maximizes power to accomplish this.

4.3 Justification for Intervention

CBT is a well-established intervention for management of acute and chronic pain in adolescents and has been effectively delivered using digital technologies to improve access to evidence-based care (2). We have had tremendous success in our research studies reaching youth with chronic pain using internet and smartphone technologies, including those in rural areas and with health disparities who do not have access to specialist services (54, 72, 73, 75). CBT interventions are flexible and can be delivered in brief treatment protocols. Our WebMAP intervention teaches six different cognitive and behavioral skills focused on

4.4 End-of-Study Definition

Once the final enrolled participant (target: 80) has completed their 6 month follow-up assessment (T4), all data collection for the study will be complete.

5 STUDY POPULATION

5.1 Inclusion Criteria

(a) age 12 to 17 years, (b) diagnosed by the attending pain physician with a primary pain disorder involving abdominal, headache, or musculoskeletal pain, (c) pain duration > 3 months, (d) average rating ≥ 5 on two items from the Brief Pain Inventory asking about average pain intensity and activity interference in the past week (0-10 scale), and (e) has access to the Internet. Youth on a stable dose (x 2 months) of medications (antidepressants, anticonvulsants, etc) for pain or sleep will be eligible.

5.2 Exclusion Criteria

(a) diagnosis of a comorbid serious health condition (e.g., cancer), (b) parent or adolescent does not speak English, (c) has active psychosis or suicidal ideation, (d) is currently taking stimulating medications, and (e) has a diagnosed primary sleep disorder (e.g., sleep apnea, narcolepsy).

5.3 Lifestyle Considerations

N/A

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include terminating use of stimulating medications. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

1. Our target sample size includes 80 adolescents ages 12-17 of any sex, race and ethnicity. Based on the percentage of eligible participants in previous studies with similar criteria, we anticipate that we will need to screen 100 participants in order to reach our target sample size of 80 adolescents.

a. Regarding the NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research:

i. Our sample will include female children/adolescents and mothers or female caregivers. We anticipate a large proportion of child and caregiver participants to be female – in previous studies with a similar population, 74% of child participants and 90% of parent participants were female.

ii. Our sample will include minorities. Specifically, we estimate enrolling participants at the following rate: 11.0% Hispanic/Latino and 89.0% not Hispanic/Latino. In terms of racial categories, we
expect to enroll participants in the following proportions: 78.4% White, 7.0% Asian, 4.0% More than One Race, 9.0% Black or African American, 1.4% American Indian/Alaska Native, and 0.2% Native Hawaiian or Other Pacific Islander. Referrals will come from the Seattle Children's Pain Clinic.

Iii. Participants will be recruited via referral from providers at Seattle Children's Pain Clinic and via EMR review. Health care providers will inform patients and families about the study and provide families with study information in the form of a flyer. Providers will then ask families if they are willing to be contacted by research staff to assess interest in the study and discuss participation. The provider will refer interested, potentially eligible participants by entering participant and parent names and contact information into a secure REDCap database hosted at SCH, or may send the referral by secure fax, email, or voicemail. Families who do not give permission for their information to be shared with SCH by the referral site may still contact SCH staff or submit their information to SCH via a secure link on the study website (self-referral), or via email or secure voicemail.

iv. Participants will be individually compensated after each completed study assessment. At each time point the child will have an opportunity to earn a $40 Amazon gift card for completing that assessment. With four time points, the child can earn up to $160 if all assessments are completed. Participants will not receive additional reimbursement for completing the intervention.

v. We will utilize standard procedures to maximize retention rates for this trial, incorporating the following elements:
a. Creation and use of a detailed contact protocol to specify when participants should be contacted throughout different study phases
b. Staff will build rapport with family – consistent contact with the same research coordinator(s)
c. Open communication with family re: contact preferences (time, method)
d. Use of varied contact methods according to family preference, study timeline, and past contact history (text, email, phone, app-based reminders and encouragement)
i. Text and email communication (based on templates) from the study team will be used for the following types of situations: initial & follow-up recruitment messaging, consent call information and scheduling/rescheduling, missing survey question follow-up, survey completion reminders, diary survey completion reminders, gift card distribution, incomplete baseline surveys, website/app login instructions, website/app usage reminders, check-ins, and updates, discharge survey follow-up, and assessment start date scheduling
e. Use of adequate incentives for survey and diary completion
f. Frequent reminders for survey and diary completion; discussion with family of assessment timelines and start dates to ensure they work with family schedule

g. Frequent monitoring of program usage and reminders via app and text/email/call as needed to encourage program adherence
mobile app)

vi. Seattle Children’s research staff will screen each completed survey for any items that were not filled out by the participant. Seattle Children's research staff will then follow up with the participant to recover information for missed questions unless the participant skipped that question intentionally.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 Study Intervention(s) or Experimental Manipulation(s) Description

All youth and parents will receive access to the WebMAP program, which consists of two separate, password-protected web programs, one for teens and one for parents completed in an 8 week period. The program design and treatment content of WebMAP follow cognitive-behavioral, social learning, and family systems frameworks. The eight adolescent modules include: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) deep breathing and relaxation, 4) implementing coping skills at school, 5) cognitive skills (e.g., reducing negative thoughts), 6) lifestyle interventions, 7) staying active (e.g., pleasant activity scheduling), and 8) relapse prevention. The eight parent modules are: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) operant strategies I (using attention and praise to increase positive coping), 4) operant strategies II (using rewards to increase positive coping and reach school goals), 5) modeling, 6) lifestyle, 7) communication, and 8) relapse prevention.

The program is designed to enhance pain self-efficacy, defined as perception of one's ability to successfully carry out daily activities while in pain, and to promote activity participation. Youth set structured and personalized goals aimed at improving their pain and functioning. Given the importance of homework and practice to behavior change, several components (e.g., positive feedback loops) actively encourage user attention and motivation in order to promote skills acquisition and rehearsal. Using a diary function on the web site, youth track their symptoms in real-time and can generate customized reports and graphs from their data. The web site uses a multimedia-rich format (e.g., animations, videos, audio clips) to deliver content. The website is built on a responsive platform and can be viewed on multiple devices (e.g., smartphones, laptops, tablets) to increase ease and flexibility of use. All website content is (a) written at a grade 5-6 reading level, (b) developmentally appropriate for the full age range of youth, and (c) is based on a unifying theme/narrative.

6.2 Measures to Minimize Bias: Randomization and Blinding

After baseline assessment is completed, participants will receive access to the study intervention. Research staff will set up accounts and instruct the participants regarding how to access the WebMAP intervention. There is no masking as this is not a randomized trial.

6.3 Study Intervention/Experimental Manipulation Adherence

Treatment is consistently delivered via the web programs. Study staff ensure that each participant has downloaded and set up the intervention program within 7 days of completing the baseline assessment. The web programs track each time a parent or youth uses the program and document when lessons are completed. The primary measure of adherence will be the number of modules
completed.

6.4 Concomitant Therapy

We will collect information from parents after each treatment phase on mental health services that may qualify as concomitant therapy. Parents report on if their teen received mental health services, if services were for pain management, if services were related to a pre-existing problem, and how many sessions their teen had.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention/Experimental Manipulation

Not applicable – this is a minimal risk, adjunctive educational intervention that provides cognitive and behavioral skills for pain management.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants may withdraw from the study or intervention voluntarily at any time. Participants may be discontinued from the study per investigator discretion if they do not complete the baseline assessment, develop a new complex medical condition (e.g. new cancer diagnosis),.

7.3 Lost to Follow-Up

Seattle Children's research staff will attempt to collect data from enrolled participants who we are unable to reach or have not completed prior assessments. Staff will follow a detailed contact protocol to contact participants at regular intervals appropriate for their study timeline and utilize a variety of contact methods according to participant preference to maximize participant retention and engagement.

8 STUDY ASSESSMENTS AND PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

Assessments will occur at baseline (T_1), immediately after intervention (2 months; T_2), and repeated at 6 months (T_3). Mediators will be assessed at an additional mid-treatment (4 weeks) data point. The intervention phase will last 2 months (8 weeks). All questionnaires will be administered using Research Electronic Data Capture (REDCap), a secure web-based tracking and on-line data acquisition system (40). We have used this system successfully in multiple studies to date. Estimated time burden is 10 minutes for parents and 40 minutes for teens. Response burden is minimized by the online administration, which allows saving and storing of responses.

Screening Measures. Participants will complete the Pediatric Sleep Questionnaire (41) to screen for sleep-disordered breathing. If they screen positive they will be referred for clinical evaluation and will not be enrolled. Parents will complete a Demographic Questionnaire to assess sociodemographic variables and pain history.

Mediators. Positive and negative affect will be assessed with the Positive and Negative Affect Scale-Child version (PANAS-C; (48). The PANAS-C consists of two mood scales with 10-items each rated on a 5-point scale for assessing positive (e.g., inspired, strong) and negative affect (e.g., guilty, scared). Both scales are internally consistent, uncorrelated, and stable over a 2-month time period; good convergent and discriminant validity have also been demonstrated (48). Executive functioning will be assessed with the Behavior Rating Inventory of Executive Function (BRIEF-2) (49), a short 12-item well validated self-report measure that assesses executive function behaviors (e.g., inhibitory control, working memory, planning and organization) in home and school environments providing three indices of regulation, Behavioral, Emotional, and Cognitive.

Sleep Measures. We will conduct a rigorous and comprehensive assessment of sleep patterns and behaviors to assess disrupted sleep, amount of sleep, sleep quality, and insomnia symptoms. Adolescents will complete validated self-report questionnaire measures, 7 days of actigraphic monitoring, and a sleep diary. Actigraphic monitoring. Youth will complete 7-days of actigraphic monitoring at each time point with the Actiwatch-2 (AW2; Phillips Respironics, MiniMitter Company Inc., Bend, OR). We will mail an Actiwatch to each participant's home (along with written instructions) using the same procedures that we successfully applied in our prior projects. Averages will be computed across the 7-day periods. We will use three variables in our analyses: minutes of estimated sleep, wake time after sleep onset and sleep efficiency, providing estimates of the amount of sleep and disruption to sleep. Subjective measures. The short form of the Adolescent Sleep Wake Scale (ASWS) is a 10-item measure of sleep quality validated in adolescents with chronic pain and other medical conditions (42). A total score indicates overall perception of sleep quality. Youth will also complete the 7-item Insomnia Severity Index (43) to specifically measure severity of insomnia symptoms. *Although developed*

for adults, the ISI has shown strong validity and reliability estimates in adolescents in our own and other's published work, e.g., (44). Total scores above 8 on the ISI indicate risk for clinically significant insomnia. Diary ratings. A sleep diary will be administered to assist with actigraphy scoring, to provide information on sleep and wake times, and to collect daily sleep quality ratings. Youth will complete the diary at bedtime and upon waking. Each morning youth will rate global sleep quality on an 11-point NRS. We have used this method in prior studies achieving high compliance (over 85%) in completing a minimum of 5 of 7 days of diary entries.

Self-management processes. Using Common Data Elements for Self-Management, 3 self-management processes will be assessed. Pain self-efficacy. The Pain Self-Efficacy Scale (45) is a 7-item measure that assesses the child's beliefs in carrying out activities when in pain. The scale has demonstrated good internal consistency, cross-informant reliability with parent report, and strong construct validity. Patient activation. The Patient Activation Measure (46) is a 13-item questionnaire that assesses an individual´s knowledge, skill and confidence for managing their health and health care. The PAM uses a 0-100 scale resulting in 4 levels of activation, from low (1) to high (4). The measure is not disease specific, and has been successfully used with a wide variety of chronic conditions. Although developed for adults, the PAM has been used in children ages 12 and above, is reliable, and shows strong construct validity. Self-management skills. The Transition Readiness Assessment Questionnaire 3.0 (47) is a 14-item measure that assesses self-management skills related to healthcare interactions, self-advocacy, and decision-making. The TRAQ has been validated in children 12-18 years with a broad range of health conditions, has good reliability and strong construct validity.

Pain and Health Outcome Measures. We will measure daytime function and health outcomes using well-validated instruments. WebMAP has diary assessments programmed into the web site to prospectively collect pain intensity and pain-related disability data over 7-day periods. Child pain intensity will be rated on the online diary using an 11-point NRS (50). The CALI is a validated instrument of pain-related disability measured by youth difficulty in performing usual daily physical, social, and recreational activities (e.g., going to school, running, walking) due to pain (51). We will measure fatigue using the PedsQL Multidimensional Fatigue Scale (52), which yields three scores for general fatigue, cognitive fatigue, and sleep-rest fatigue. It has been widely used in many pediatric chronic health conditions demonstrating strong reliability and validity. Global health will be assessed with the PROMIS pediatric global health measure (53), a 7-item measure summarizing a child's physical, mental, and social health into a single score. Concurrent validity has been recently demonstrated with lower scores for children with chronic conditions and strong relationships with measures of positive health.

Treatment engagement, adherence, and acceptability. Treatment engagement will be measured by completion of at least 1 module while adherence is defined as the completion of 6 or more modules. The administrative interface of the WebMAP program has a tracking system in place for recording each time a user logs onto the program. Each module contains multiple-choice quizzes concerning the content presented as well as behavioral assignments, fill-in-the-blank fields, and use of the diary tracker. Data fields completed within modules are stored, generating a comprehensive activity record of module specific use including self-management tasks. Treatment acceptability and satisfaction will be assessed with the Treatment Evaluation Inventory (54), which we have adapted for pain self-management, and ratings of global

impression of change.

8.2 Safety Assessments

This study aims to understand how sleep deficiency influences youth's ability to engage with, implement, and benefit from a pain self-management intervention. We will study a cohort of 80 youth, ages 12 to 17 years, with chronic musculoskeletal, head, or abdominal pain. Assessments will occur at baseline, immediately after intervention, and repeated at 3 months post-intervention. Mediators will be assessed at an additional mid-treatment (4 weeks) data point. All youth will receive an internet-delivered pain self-management intervention (WebMAP) over an 8-week period. Following the recommended Common Data Elements for self-management we measure three self-management processes including patient activation, pain self-efficacy, and self-management skills, and assess patient-reported outcomes of health (global health, fatigue) and pain (pain symptoms, pain-related disability). Positive and negative affect will be assessed as potential mediators. Sleep deficiency will be comprehensively assessed with subjective measures, daily sleep logs, and ambulatory actigraphy monitoring to measure disrupted sleep, amount of sleep, sleep quality, and insomnia symptoms. The risks of this intervention are well known from prior studies using this intervention, and they are minimal. Participants will receive their usual medical treatment during the study and thus will be monitored by their treating physicians. Given this study profile, we propose the following Data and Safety Monitoring Plan which has been approved by our Institutional Review Board (approval date: 4/19/18).

We will of course comply with any additional requirements or changes to the plan that the National Institute of Nursing Research (NINR) request prior to the study initiation.

1. **Monitoring entity.**

Overall responsibility for data and safety monitoring lies with the PI, Dr. Tonya Palermo, a licensed clinical psychologist and expert in pediatric pain management, who will be aided by co-investigator, Teresa Ward, MSN, PhD, a nurse scientist with clinical expertise as a nurse practitioner in a pediatric sleep disorders center. In addition, the study will use a Safety Monitoring Committee (SMC) consisting of two independent investigators: Dr. Susan McCurry, a clinical psychologist and sleep specialist who works in the School of Nursing Northwest Research Group on Aging team and Dr. Pingping Qu, biostatistician at SCRI and expert in longitudinal analysis. Given that the intervention is low risk and this is a single site study without random assignment or blinding we believe this level of monitoring is appropriate for this protocol. Specifically, the role of the SMC is to ensure the safety of participants, the validity and integrity of the data, the conduct of the study, and the availability of data in a timely manner, as well as, recommend appropriate action regarding adverse events or other safety issues. Dr. Palermo is responsible for reporting serious adverse events to NIH.

2. **Procedures for monitoring study safety, minimizing research-associated risk, and protecting confidentiality**

Monitoring study safety: Monitoring study safety will occur from the initial screening, throughout the informed consent process, and through study completion. Weekly monitoring of participants and internal monthly quality audits for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance. The PI will report all serious and/or unexpected adverse events to the IRB, the SMC, and the NINR within 48 hours after identification.

The PI will be responsible for the day-to-day trial management of this study. The Clinical Research Associate and Psychology Fellow, under the PI's supervision, will use an Access database checklist to ensure that all study procedures are being followed (including consents) and that all surveys are being completed according to schedule. Study staff will log onto the administrative website of the intervention program each day to review study participant data and to download their study assessments. The PI will monitor for the responses that are spontaneously reported by children or parents. In the case of critical event, the PI (or a designated covering investigator, if Dr. Palermo is not available) will stop the intervention and will be available 24 hours a day to be called via cell phone to address questions. These are reviewed immediately with the clinically responsible PI and/or Co-I. All actions taken will be documented on a case report form.

Minimizing research-associated risks: Meticulous monitoring of study safety will be conducted by the PI (Palermo), Co-Investigators, and the Safety Monitoring Committee. All appropriate steps will be taken to maintain the security of participant data. All participant raw data will be coded and stored separately from identifying information on a password protected server to which only study staff has access. Online data will be saved in a secure password protected database that is protected by the highest standards for electronic data safety. The data stored on the central server will be automatically coded with participant ID and no personal identifiers will be associated with these data. Study personnel will be able to access the data on the central server using a login and password in order to track compliance.

The occurrence of any adverse event will be assessed weekly at study meetings. Study personnel will review the event forms from the previous week for events that were reported as new. The investigators will follow all adverse events until the point of a satisfactory resolution. Study safety, risk and reports of other problems (issues not meeting criteria for a serious adverse event) will be reviewed at quarterly meetings with the PI, Co-Investigators, and an action plan to address any identified issue will be developed and monitored by the Safety Monitoring Committee. The PI will comply with all requirements of the IRB for the reporting of safety data and adverse/serious adverse events. The PI will report all serious and/or unexpected adverse events to the IRB, the SMC, and the NINR within 48 hours after identification. The PI will provide a discussion of any adverse events occurring in the course of the study to the IRB on an annual basis. All adverse events experienced by study participants from the date of enrollment through the completion of the study will be reported. All adverse events regardless of attribution to treatment procedures will be collected and recorded. Participants will be asked in an open-ended way about the presence of any adverse events. The likelihood that the event is related or not related to treatment will be noted.

Protection of confidentiality of participants' data: Data quality will be ensured by having trained staff demonstrate compliance with study protocol to include auditing selected cases (10%) for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance with all human subjects and HIPAA requirements. Data quality will also be ensured by having each completed survey checked to minimize missing data. The Research Associate will also keep track of reasons for missing data in the Access database. In order to have the most complete data for analysis, a benchmark of success will be to have complete data on >95% of subjects retained to study completion.

Errors in data capture, entry and analysis will be greatly reduced by the use of REDCap which alerts the participant and research staff to missed or implausible questionnaire responses. REDCap also provides output results into a file easily imported into SPSS, where SPSS syntax can autoscore the questionnaire responses, greatly reducing scoring errors. All data manipulation is recorded by REDCap. It is standard procedure in the PI's laboratory that all data manipulation and transfer is always double checked by another research staff member, who is required to sign off on the double check. We also note that the Office of Research Compliance at Seattle Children's Hospital audits all research studies at least once, and PIs and research staff are continually educated on research best practices.

The Web-based electronic data management system is password protected and encrypted, no direct identifiers will be present among electronic data. The code that links identifying information will be accessible only to study staff and will be kept in a locked office in a locked file, separate from data collected during the course of the study and separate from the link between study data and subject identity. Confidentiality of research data will be protected as described in the Human Subjects' Section of the Application.

3. **Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems**:

The PI will comply with all requirements of the IRB for the reporting of safety data and adverse/serious adverse events. The PI will report all serious and/or unexpected adverse events to the IRB, the SMC, and the NINR within 48 hours after identification. In the event that a subject withdraws from the study or the investigator decides to discontinue a subject due to a serious adverse event, the subject will have appropriate follow-up monitoring until the problem has resolved or stabilized or is determined to be unrelated to the study.

The SMC will review all adverse events and unanticipated events within 48 hours and will discuss them to determine the likelihood that the serious adverse event is related to involvement in the research. They will also review all study-related data on a semi-annual basis in a safety monitoring meeting to review information related to the safety of study participants and summarize any adverse events.

Dr. Palermo, as PI, will provide timely reporting to the funding agency of: any unanticipated problems or serious adverse events that may be related to the study protocol; any IRB-approved revisions to the

study protocol that change the risk for participants; any action taken by the IRB regarding the research activity and any response to those actions; and a summary of recommendations made by the safety monitoring committee and any action plan for response.

Additionally, all adverse events, serious and non-serious, and unanticipated problems as defined in the HHS guidance (http://www.hhs.gov/ohrp/policy/advevntguid.html), will be reported annually to the IRB during the yearly renewal processes. The PI will generate and submit to the above entities a report that will be masked to minimize inclusion of information that can link the event to a specific person.

d. For multisite studies, procedures to ensure compliance with the monitoring plan and reporting requirements across study sites.
NA. This is not a multi-site trial

e. An assessment of external factors that may have an impact of the safety of participants or on the ethics for the research study
The research procedures and treatment involve minimal risk. Dr. Palermo keeps abreast of the literature and attends scientific meetings to stay informed of developments in pain and sleep treatments in children to learn about factors that may change the identified risks or possible benefits to participants. In the unlikely event that new information that might alter the risk of research procedures is learned, Dr. Palermo will revise the protocol to minimize such risks and inform the IRB, SMC, and NINR. In addition, the participants will be notified of any significant new findings that develop during the course of research that may affect their wish to continue participation in the study.

f. The advanced plans for interim and/or futility analysis
Given the small scope of the study, and to preserve the statistical power, interim and/or futility analysis is/are not planned.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.3.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity

- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 Classification of an Adverse Event

To assess relationship of an event to study intervention, the following guidelines are used by the Co-PIs:

1. Related (Possible, Probable, Definite)

a. The event is known to occur with the study intervention.

b. There is a temporal relationship between the intervention and event onset.

c. The event abates when the intervention is discontinued.

d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset.

b. An alternate etiology has been established.

8.3.3.1 Severity of Event

The following scale will be used by the Co-PIs to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

8.3.3.2 Relationship to Study Intervention/Experimental Manipulation

To assess relationship of an event to study intervention, the following guidelines are used by the Co-PIs:

1. Related (Possible, Probable, Definite)

a. The event is known to occur with the study intervention.

b. There is a temporal relationship between the intervention and event onset.

c. The event abates when the intervention is discontinued.

d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset.

b. An alternate etiology has been established.

8.3.3.3 Expectedness

The study PIs will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.4 Unanticipated Problems

Unanticipated problems involving risk to human subjects will be recorded and reported throughout the entire study.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

• unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

• related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

• suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

- Primary Objective:

Aim 1. Characterize the relationship between baseline sleep deficiency and self-management processes. H1. Greater baseline sleep deficiency (shorter sleep duration, poorer sleep quality, increased insomnia symptoms, greater wake time after sleep onset) will be associated with lower activation, lower pain self-efficacy, and lower use of self-management skills from pre- to post-treatment. H2. Positive and negative affect and executive functioning will mediate the relationship between sleep deficiency and self-management processes.

- Secondary Objective:

Aim 2. Determine the effect of baseline sleep deficiency on treatment acceptability, engagement, and benefit from an internet-delivered pain self-management intervention. H3. Greater sleep deficiency will be associated with lower perceptions of treatment acceptability and engagement (fewer logins, fewer completed treatment modules and assignments). H4. Greater sleep deficiency will be associated with less benefit (fewer improvements) in ratings of global health, fatigue, pain symptoms, and pain-related disability following pain self-management intervention. *H5.* Positive and negative affect and executive functioning will mediate the relationship between sleep deficiency and treatment acceptability, engagement and benefit.

9.2 Sample Size Determination

Aim 1: A series of Monte Carlo simulations were conducted to evaluate longitudinal mediation (70). Results indicate 80% power for a sample size of 75 given a mediated effect of approximately 27% or larger and specific indirect effects of R^2 = .12 or larger.

Aim 2: A series of Monte Carlo simulations were specified (27) to evaluate power to detect variance in linear change. Results indicate a sample size of 52 is needed. Adding predictive structural paths to the simulated LGMs indicated that a sample size of N = 75 would be powered at .80 to detect an effect size as small as R^2 = .06 and .03 for the slope and intercept, respectively (71).

9.3 Statistical Analyses

Data will be reviewed for completeness and errors including consistency checks for relevant variables. Tabular and graphical methods of data exploration including frequency tables, scatterplots, and box plots will be used to explore distributions of study variables. For the primary analytic plan, we will rely

on panel and latent growth models (LGM), within the structural equation modeling (SEM) framework (55-57). Both approaches can be implemented within a manifest and/or latent variable context (58). Unlike traditional repeated-measures analysis of variance, SEM allows for a more accurate and flexible approach to analyzing repeated measures data by simultaneously modeling change in the means (fixed effects) and in the variance and covariance of initial level and change (random effects) (56, 59-61). We include biological covariates of age, sex, and pain location in all models. We expect 10% attrition for a final projected sample size of n = 72. Full Information Maximum Likelihood (FIML) estimation will be used to handle missing data related to attrition and non-response (62) incorporating robust standard errors or bootstrapping to correct for non-normality (61). FIML estimation improves accuracy and power relative to other missing data handling methods (63, 64).

Aim 1. Characterize the relationship between baseline sleep deficiency and self-management processes. We will use structural equations (65, 66) to assess interrelations, direct effects, and indirect mediation effects in a longitudinal panel model. Mediation will be tested by decomposing a total effect of each sleep deficiency measure (duration, wake time, quality, insomnia symptoms) on self-management processes into direct effects and indirect effects (65, 66). Significance tests of indirect effects will be carried out using the Monte Carlo (*empirical-M*) method to obtain 90% asymmetric confidence intervals (67-69).

Expected Results, Interpretation, and Possible Pitfalls. We expect the higher the level of sleep deficiency the higher negative affect, lower positive affect, *lower executive functioning*, lower the behavioral activation, self-efficacy, and self-regulation at baseline. There will likely be an indirect effect of sleep deficiency on affect *and executive function* and of affect *and executive function* on self-management processes. *We also expect that a significant indirect effect will indicate that sleep deficiency affects change in self-management processes by influencing affect or executive function*.

Aim 2. Determine the effect of baseline sleep deficiency on treatment acceptability, engagement with, and benefit from an internet-delivered pain self-management intervention. We will use LGMs to model individual differences in final acceptability and engagement status and the rates of change in global health, pain symptoms, fatigue, and pain-related disability (56, 59-61) and to test the proposed predictive and mediated effects.

Expected Results, Interpretation, and Possible Pitfalls. We expect that global health will improve over the course of the study while pain, fatigue, and pain-related disability will decrease. We also expect that participants will significantly vary around the average intercept and slope. We expect the higher the initial level of sleep deficiency the shallower the increase in global health over time and the shallower the decline in pain, fatigue, and pain-related disability. Across all models we expect less than 10% attrition over the course of the study based on our prior work (27). We will use the maximum likelihood estimation option in the Mplus 7.3 software program to deal with missing data and use the robust standard error option to correct for non-normality (61).

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