Effectiveness of an mHealth psychosocial intervention to prevent transition from acute to chronic postsurgical pain in adolescents

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Grantee Institution: Seattle Children's Research Institute

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the following:

- The International Council for Harmonisation Good Clinical Practice (ICH GCP) E6
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46)
- Completion of Human Subjects Protection and ICH GCP training by the Principal Investigator and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Interest
CBT	Cognitive Behavioral Therapy
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CPSP	Chronic Post-Surgical Pain
CSI	Clinical Site Investigator
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors

IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NDA	New Drug Application
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PO	Program Official, NIH
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event/Serious Adverse Experience
SCH	Seattle Children's Hospital
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	Effectiveness of an mHealth psychosocial intervention to prevent transition from acute to chronic postsurgical pain in adolescents
Précis:	This is a randomized controlled trial to test effectiveness of the SurgeryPal intervention vs. education control to improve acute and chronic pain and health outcomes in 500 youth undergoing major musculoskeletal surgery and their parents/caregivers. Youth will be randomized on an individual level using a factorial design to SurgeryPal or Education during 2 phases of intervention: 1) pre-operative phase (4 week duration delivered over the 4 weeks leading up to surgery), and 2) post-operative phase (4 week duration starting 3 weeks following surgery). Thus there will be 4 treatment arms. Participants will undergo 4 assessments, independent of their treatment assignment: T1: Baseline (pre-randomization); T2: acute post-surgery outcomes (daily assessment of acute outcomes beginning day 1 through day 14 after hospital discharge from surgery); T3: Post-surgery follow-up (assessment of chronic outcomes at 3-months post-surgery); T4: Final post-surgery follow-up (assessment of outcomes at 6-months post-surgery).
Objectives:	Primary: Determine effectiveness of a pre-operative mHealth psychosocial intervention to improve acute pain outcomes in adolescents undergoing major musculoskeletal surgery Determine effectiveness of a post-operative mHealth psychosocial intervention to improve chronic pain outcomes at 3 months in adolescents undergoing major musculoskeletal surgery. Determine the combined effects of pre- and post-operative psychosocial intervention on chronic pain outcomes. Secondary: Determine effectiveness of pre-operative psychosocial intervention to reduce opioid use during the 14 days following hospital discharge. Determine effectiveness of psychosocial intervention to improve HRQL following surgery.

Population:	The proposed study will enroll 500 adolescents ages 12-18 who are scheduled to undergo spinal fusion surgery for idiopathic/juvenile scoliosis, spondylolisthesis or kyphosis plus one parent/caregiver participant for each adolescent (for a total of 1000 subjects). Adolescents will be recruited from approximately 25 pediatric centers across the United States. Families who do not speak or understand English, or do not have access to a smart device will be excluded. Adolescents who meet any of the following criteria will be excluded: severe learning disability/cognitive impairment/intellectual delay, diagnosed unstable psychiatric condition, severe/systemic disease (e.g. neuromuscular scoliosis, cancer), taking medication daily for a medical condition (except allergies/asthma/anxiety/depression), have had a prior major surgery, or have a diagnosed chronic musculoskeletal pain condition (see 5.1 and 5.2 for more detail).
Phase or Stage:	Phase II
Anticipated Number of Sites:	approximately 30 or more
Description of Intervention/ Experimental Manipulation:	The SurgeryPal intervention is a cognitive-behavioral program for youth undergoing major surgery. SurgeryPal is delivered in two 4-week phases: the pre-operative phase, and the post-operative phase. Each phase consists of 3 separate treatment modules for youth and parents, which teach cognitive and behavioral coping skills to target known psychosocial and behavioral risk factors for poorer postsurgical outcomes (i.e. anxiety/distress and sleep), and provide training in pain self-management skills. Pre-operative modules include: 1) Preparing for surgery, 2) Coping with stress before surgery, and 3) Getting ready for the hospital. Postoperative modules include: 1) Coping at home after surgery, 2) Return to activities and school, and 3) Long-term recovery. Modules are self-guided and interactive, and focus on preparation for and recovery from surgery. The goal of the program is to improve psychosocial functioning, reduce pain, and enhance quality of life following surgery in youth.
Study Duration:	48 months
Participant Participation Duration:	7-11 months

Estimated Time to Complete Enrollment: 36 months

1.2 Schedule of Activities (SoA)

Timepoint	Timing	Participant	Location	Goal	Activities
Phase 1 Screening	4+ weeks pre-surgery	Teen, Parent	Pre-surgery clinic at referring site	Screening	Patient provider conducts initial screening in person, and introduces study
Patient referral	4+ weeks pre-surgery	Teen, Parent	Secure online portal	Referral	Referring provider submits referral information
Phase 2 Screening	4+ weeks pre-surgery	Teen, Parent	By phone	Eligibility	Primary site conducts second wave of screening, and explains study
Consent	4+ weeks pre-surgery	Teen, Parent	By phone	Consent	Consent and assent by phone; Documentation using Research Electronic Data Capture System (REDCap)
Assessment 1 (T1)	4 weeks (window 3-12 weeks) pre-surgery	Teen, Parent	Online	Baseline assessment	Completion of baseline pain and health measures using REDCap
Incentive 1	T1 complete	Teen, Parent	Email/text	Incentive payment	Participant receives gift card (all groups)
Pre-surgery intervention phase	One month duration, pre-surgery	Teen, Parent	Online	Treatment	Parents and youth (Treatment groups 2 and 4) complete 3 treatment modules; Groups 1 and 3 access education control.
Assessment 2 – Post-treatment 1 (T2-PT1)	After completion of pre-surgery intervention phase, before surgery	Teen, Parent	Online	Treatment satisfaction/ experience	Completion of treatment-related measures using REDCap
Incentive 2	T2-PT1 complete	Teen, Parent	Email/text	Incentive payment	Participant receives gift card (all groups)
Assessment 2 (T2) – daily measures	Daily measures 1-14 days after discharge; Other measures sent 1 week post discharge (window 1-3 weeks)	Teen	Online	Acute post-surgery outcomes	Daily assessment of pain, activity and medication use, completed using REDCap diaries; completion of pain and health acute outcomes measures using REDCap
Incentive 3	T2 complete	Teen	Email/text	Incentive payment	Participant receives gift card (all groups)
Post-surgery intervention phase	One month duration, after T2 complete	Teen, Parent	Online	Treatment	Parents and youth (Treatment groups 3 and 4) complete 3 treatment modules; Groups 1 and 2 access education control.
Assessment 3 - Post-treatment 2 (T3-PT2)	After completion of post-surgery intervention phase	Teen, Parent	Online	Treatment satisfaction/ experience	Completion of treatment-related measures using REDCap
Incentive 4	T3-PT2 complete	Teen	Email/text	Incentive payment	Participant receives gift card (all groups)
Assessment 3 (T3) – daily measures	3 months (window 12-16 weeks) post-surgery	Teen, Parent	Online	Post-surgery follow-up	Daily assessment of pain, activity and medication use, completed using REDCap diaries; Completion of pain and health

Timepoint	Timing	Participant	Location	Goal	Activities
					measures using REDCap
Incentive 5	T3 complete	Teen, Parent	Email/text	Incentive payment	Participant receives gift card (all groups)
Assessment 4 (T4) – daily measures	6 months (window 6-8-months) post-surgery	Teen, Parent	Online	Final post-surgery follow-up	Daily assessment of pain, activity and medication use, completed using REDCap diaries; Completion of follow-up pain and health measures using REDCap
Incentive 6	T4 complete	Teen, Parent	Email/text	Incentive payment	Participant receives gift card (all groups)

1.3 Background Information

Major musculoskeletal surgeries are associated with particularly high prevalence of both acute and chronic postsurgical pain (CPSP), with 80% of youth reporting intense acute pain after hospital discharge (83), and up to half reporting CPSP up to one year after spine surgery (82). Further, chronic pain during adolescence can extend into adulthood (47), generating lifelong consequences on functioning, productivity, and quality of life, as well as increasing risk for substance use disorder (106). Interventions to improve recovery and reduce pain after surgery have potential to interrupt a negative trajectory of suffering and disability associated with chronic pain. Adolescents undergoing major surgeries urgently need effective therapies to reduce pain and exposure to opioids, to mitigate potential for addiction.

In our own research, high adolescent anxiety, sleep disturbance, low pain self-efficacy, and high parent anxiety/distress were associated with higher intensity pain and poorer HRQL at both short- and long-term follow-up after major surgery (18, 33, 68, 83, 87, 88). Moreover, others have found that higher adolescent anxiety before surgery is associated with increased opioid consumption at home following major musculoskeletal surgery (38, 104). Taken together, this body of research demonstrates that psychological and behavioral factors underlie persistent pain and opioid use following surgery, and a biopsychosocial approach to perioperative care is critically needed.

There is a large body of evidence for the efficacy of psychosocial interventions in reducing pain and disability in adolescents with a range of chronic pain conditions. These programs include self-management interventions such as pain education, relaxation training, and other cognitive-behavioral strategies (CBT). In the context of surgery, pre-operative psychosocial interventions have been shown to reduce acute post-operative pain intensity (22, 52). Similarly, pain self-management strategies (imagery, relaxation strategies) taught after surgery reduce pain intensity during the weeks following surgery (12). From prior studies it is not clear when to deliver psychosocial intervention (pre-operative or post-operative), which is important for building proper implementation approaches. In order to address this gap in knowledge that prevents changes in clinical practice, randomized controlled trials are needed to establish the effectiveness of CBT interventions to reduce opioid use

and prevent CPSP in adolescents, and to evaluate optimal timing of intervention delivery.

Major barriers exist for adolescents to access CBT due to the geographical distance and limited scheduling that prevents most patients from receiving psychological intervention (74, 77). eHealth and mHealth chronic pain self-management interventions have been found effective in both adult and pediatric populations (2) for managing pain and disability. 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).

We will apply these technologies to provide a perioperative CBT program called “SurgeryPal” for adolescents undergoing musculoskeletal surgery that will emphasize empowerment, parent involvement, and offer pain coping skills, to promote recovery following surgery. This study will begin to address the gap in interventions provided to adolescents to address risk for CPSP. Demonstration of the effectiveness of this intervention to improve clinically meaningful outcomes will transform the current approach to clinical care, advancing perioperative management to integrate a biopsychosocial approach into practice and reduce reliance on opioids. This scalable intervention will allow for broad implementation in pediatric spine centers across the country. In addition, our RCT is designed to explore mechanisms underlying treatment effect, which will advance our understanding of the transition from acute to chronic pain. This research aligns with the Federal Pain Research Strategy to optimize management of pain across the continuum of acute to chronic pain in patients across the lifespan (99).

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Rationale

1 million youth undergo major surgery each year in the United States. After major musculoskeletal procedures, 80% of adolescents experience moderate-severe acute postoperative pain at home 2 weeks following hospital discharge. Additionally, 20% of youth develop chronic pain after major surgery, or as high as 50% following spine fusion surgery. Psychosocial factors predict chronic pain, however, the current perioperative standard of care is based solely on a medical model, relying on opioids for pain treatment. A biopsychosocial approach to perioperative care is critically needed in order to reduce opioid use and prevent chronic postsurgical pain. Research has demonstrated the efficacy of psychological interventions in reducing acute postoperative pain and pain several weeks following surgery, however, there is a lack of evidence regarding clinically important long term outcomes and a lack of information regarding when it is ideal to deliver psychosocial interventions (pre- vs. post-operative).

Aim 1. Determine effectiveness of a pre-operative mHealth psychosocial intervention to improve acute pain outcomes in adolescents undergoing major musculoskeletal surgery.

H1: Youth receiving pre-operative CBT (arms 2&4) will have a faster rate of recovery (acute pain intensity and interference: primary outcomes), as well as lower opioid use during the 14 days following hospital discharge, compared to youth who receive pre-operative education (arms 1&3).

Aim 2. Determine effectiveness of a post-operative mHealth psychosocial intervention to improve chronic pain outcomes at 3 months in adolescents undergoing major musculoskeletal surgery.

H2: Youth receiving post-operative CBT only (arm 3) will have lower chronic pain intensity and interference (primary outcomes) compared to youth receiving education control (arm 1).

Aim 3. Determine the combined effects of pre- and post-operative CBT on chronic pain outcomes.

H3: Youth receiving both phases of perioperative CBT (arm 4) will have lower chronic pain intensity and interference (primary outcomes), as well as higher quality of life, and lower psychosocial distress, sleep disturbance, and opioid misuse compared to youth receiving single phase intervention or education control at 3 months (arms 1,2,3).

Aim 4. Explore mechanisms of an mHealth psychosocial intervention to prevent CPSP.

H4: Youth receiving combined pre- and post-operative CBT (arm 4) will have lower rates of CPSP compared to arms 1, 2, and 3.

H5: Reductions in acute postsurgical pain will mediate treatment effects on reducing incidence of CPSP.

H6: Changes in sleep quality, anxiety and depression, and pain catastrophizing from baseline to 3 months will mediate effect of treatment on pain outcomes at 6-months.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

Risks for this study concern the potential for emotional distress, loss of confidentiality, and a burdensome time commitment. Study questionnaires and the mobile app/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 and the Data Coordinating Center (DCC) at the University of Utah, which is providing data management in collaboration with the Seattle research team. 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 referral sites 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.

2.2.2 Potential Benefits

Participation in this research may or may not benefit the participant. Completion of the CBT program delivered via the app may help to reduce pain and improve functioning in adolescents who receive this treatment. Information collected will provide useful data regarding perioperative delivery of psychosocial treatment in adolescents at risk for postsurgical pain that may inform implementation of effective treatments for adolescents undergoing major surgery. After the study is completed and results are published, we will send participants an email about what we learned. The potential risks of

participation to the participants are considered to be minimal in relation to the potential gain in critical knowledge of the effectiveness of perioperative psychosocial intervention to improve pain outcomes in youth undergoing major surgery.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary

Primary Outcomes: Aim 1 (T2/ Acute Phase): Acute Pain Intensity and Interference: this will be measured using a patient-reported outcome measure, the 11 item Brief Pain Inventory. This measure has 2 scales: pain intensity (4 items) and pain interference (7 items). The 24 hour (short) version of this measure will be completed via REDCap daily for 14 days beginning on day 1 after hospital discharge, and individual rate of recovery will be computed for each participant over 14 days to yield the primary acute pain outcome measure for Aim 1.

Primary Outcomes: Aims 2 and 3 (T3/ Chronic Phase): Chronic Pain Intensity and Interference: this will be measured using a patient-reported outcome measure, the 11 item Brief Pain Inventory. This measure has 2 scales: pain intensity (4 items) and pain interference (7 items). The 24 hour (short) version of this measure will be completed via REDCap daily for 7 days beginning 3 months after the participant's surgery date, and will be averaged for each participant over 7 days to yield the primary chronic pain outcome measure for Aims 2 and 3.

Objective	Brief Description of Outcome Measure	Outcome Measured By	Time Frame
ASSESSMENT TIME POINT: **T1 = pre-randomization baselinebefore surgery** **T2 = post-treatment surveys (PT1) delivered after pre-surgery intervention phase and before surgery; acute outcomes, daily measures 1-14 days after hospital discharge;** **T3 = post-treatment surveys (PT2) delivered after post-surgery intervention phase; chronic outcomes, 3 months post-surgery** **T4 = final follow up, 6 months post-surgery**			
Determine effectiveness of a pre-operative mHealth psychosocial intervention to improve acute pain outcomes in adolescents undergoing major musculoskeletal surgery	The Brief Pain Inventory Short Form assesses self-reported acute pain intensity, pain interference and medication use in a 24-hour timeframe. Questions evaluate worst, least, average, and current pain intensity, pain interference with sleep, mood, walking ability, general physical activity, work/school, relationships, and enjoyment of life.	Brief Pain Inventory Short Form Pain Severity and Pain Interference Scales (Teen Report)	Daily for 14 days on days 1-14 post-hospital discharge (T2)

Objective	Brief Description of Outcome Measure	Outcome Measured By	Time Frame
Determine effectiveness of a post-operative mHealth psychosocial intervention to improve chronic pain outcomes at 3 months in adolescents undergoing major musculoskeletal surgery.	The Brief Pain Inventory Short Form assesses self-reported acute pain intensity, pain interference and medication use in a 24-hour timeframe. Questions evaluate worst, least, average, and current pain intensity, pain interference with sleep, mood, walking ability, general physical activity, work/school, relationships, and enjoyment of life.	Brief Pain Inventory Short Form Pain Severity and Pain Interference Scales – (Teen Report)	Daily for 7 days at T3
Determine the combined effects of pre- and post-operative CBT on chronic pain outcomes.	The Brief Pain Inventory Short Form assesses self-reported acute pain intensity, pain interference and medication use in a 24-hour timeframe. Questions evaluate worst, least, average, and current pain intensity, pain interference with sleep, mood, walking ability, general physical activity, work/school, relationships, and enjoyment of life.	Brief Pain Inventory Short Form Pain Severity and Pain Interference Scales (Teen Report)	Daily for 7 days at T3

3.2 Secondary

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Determine effectiveness of psychosocial intervention to improve HRQL following surgery (Aim 3).	15-item measure assessing self-reported physical, social, and emotional health-related quality of life over the last 7 days. Pain intensity and PedsQL will be used to define a binary variable for presence of chronic postsurgical pain.	Pediatric Quality of Life Inventory - Short form, acute version (PedsQL) (Teen Report)	T1, T3, T4
Determine effectiveness of pre-operative psychosocial intervention to reduce opioid use.	Youth will report medication use on the BPI, including selecting medication name from a dropdown list (opioid, acetaminophen, anti-inflammatory, other).	Brief Pain Inventory medication use items (Teen Report)	T1, T2, T3, T4
Determine effectiveness of psychosocial intervention to reduce opioid misuse following surgery (Aim 3).	This tool adapted for self-report in children age 11-17 by the American Psychiatric Association (40), and recommended by the National Institute on Drug Abuse for substance use screening in adolescents, will be used to assess alcohol, smoking, substance, and opioid use (43) (65). Additional questions on reasons for misuse (e.g. to treat pain, to get high, etc.) and source of opioids (e.g. prescription, from a friend or relative) will be collected using the corresponding questions and response options used in the National Survey on Drug Use and Health.	The American Psychiatric Association Adapted NIDA Modified ASSIST Tool 2 (Teen Report)	T1, T3, T4
Determine effectiveness of perioperative psychosocial intervention to reduce psychosocial distress after surgery (Aim 3).	This measure assesses parent and youth self-reported anxiety (fear, anxiety, hyperarousal, and somatic symptoms) and depression (negative mood, negative views of self, and negative social cognition, decreased positive affect and engagement).	PROMIS Anxiety 8a and Depression 8a Instruments (Teen Report)	T1, T3, T4
Determine effectiveness of perioperative psychosocial intervention to improve mental health in parents after surgery (Aim 3).	A 4 item screening measure of general anxiety and depressive symptoms	PHQ-4 (GAD-2 and PHQ-2) (Parent Report)	T1, T3, T4

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Determine effectiveness of perioperative psychosocial intervention to reduce psychosocial distress in children after surgery.	A 4-item measure that screens for anxiety and depressive symptoms.	PHQ-4 (GAD-2 and PHQ-2) (Teen Report)	T1, T3, T4
Determine effectiveness of perioperative psychosocial intervention to improve sleep quality.	This 10–item measure assesses self-reported sleep quality. 4 additional items assess sleep duration on weekdays and weekends.	Adolescent Sleep Wake Scale 10-item version –(Teen Report)	T1, T3, T4
Determine effectiveness of perioperative psychosocial intervention to reduce pain catastrophizing.	Self-report 13 item measures that assess child pain catastrophizing and parent's catastrophizing about child's pain, respectively.	Pain Catastrophizing Scale – Child Version (Teen Report); Pain Catastrophizing Scale – Parent Version (Parent Report)	T1, T3
Determine effectiveness of perioperative psychosocial intervention to reduce global pain severity.	A 1-item measure that assesses adolescent's self-reported global impression of pain severity.	Patient Global Impression of Severity Scale (Teen Report)	T2, T3, T4
Assess baseline pain severity and interference.	The Brief Pain Inventory Short Form assesses self-reported acute pain intensity, pain interference and medication use over the past 7 days. Questions evaluate worst, least, average, and current pain intensity, pain interference with sleep, mood, walking ability, general physical activity, work/school, relationships, and enjoyment of life, as well as non-opioid and opioid analgesic use.	Brief Pain Inventory Short Form Pain Severity and Pain Interference Scales (Teen Report) – 7 day recall	T1 (completed once)
Assess treatment satisfaction and acceptability for a perioperative psychosocial intervention.	An adapted self-report measure specific to pediatric postsurgical pain that will collect parent and youth assessments of acceptability and satisfaction with the intervention's content and management approach	Treatment Evaluation Inventory, short form (Teen and Parent Report)	T2 (PT1), T3 (PT2)

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess treatment engagement for a perioperative psychosocial intervention.	The mobile application and website will track each time a parent or youth uses the program. Treatment adherence will be collected by assessing number of completed modules/lessons.	Mobile application, website use	During assigned pre- and post-op treatment phases)
Collect information on concomitant therapy.	We will collect information from parents at each assessment on use of concomitant therapy (e.g. psychosocial interventions that the adolescent received during the pre- or post-operative period to prepare for surgery).	Concomitant Therapy Questionnaire (Parent Report)	T2 (PT1), T3 (PT2)
Report treatment experience.	A self-report scale with open ended questions and ratings of reactions to the treatments (e.g., stress, technical issues) from parents and youth.	Treatment Experience Questionnaire (Teen and Parent Report)	T2 (PT1), T3 (PT2), T4
Collect sociodemographic information.	Parents report on participants' sex, gender, race and ethnicity, family income, parent education, ZIP code, and youth's pain history.	Demographic Form (Parent Report)	T1

3.3 Tertiary/Exploratory

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Explore mechanisms of an mHealth psychosocial intervention to prevent CPSP: a. compare rates of CPSP among youth receiving combined pre- and post-operative CBT (arm 4) to youth in arms 1, 2, and 3; b. examine mediation of treatment effects on CPSP via changes in acute postsurgical pain.	CPSP will be assessed as a binary outcome defined as pain that interferes with HRQL. Pain intensity will be assessed using a 0-10 NRS averaged over 7 days. HRQL will be assessed with the PedsQL – Short Form.	Pain intensity 0-10 numeric rating scale (NRS) for average pain in past 24 hours (from BPI), and PedsQL – Short Form (Teen Report)	T3 and T4; pain intensity assessed daily for 7 days at each timepoint.
Characterize adolescent opioid use history.	Parents report on if their child has ever had a prescription for opioids, and if so, when and why their child was prescribed opioids.	Parent opioid question	T1

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Characterize adolescent lifetime misuse of opioid prescriptions, pain relief expectancy, and pain expectancy.	A single item from the Youth Risk Behavior Surveillance System (YRBSS) assesses how many times adolescents have misused opioids. Additional items assess expectations about the pain levels after surgery and pain medicine relief after surgery.	YRBSS question re: lifetime opioid misuse. Pain expectancy: 0-10 NRS. Pain medicine relief expectancy: 11-point scale from 0% - no relief to 100% - complete relief.	T1
Explore adolescent pain relief preferences.	Teen participants endorse five risk-benefit items (e.g., “Having side effects from medicine is a bigger problem than having pain”) from strongly disagree (−2) to strongly agree (+2). This measure was adapted for ages 12-18.	Adolescent Pain Relief Preferences Survey	T1, T3
Explore adolescent perceptions regarding the riskiness of over the counter/opioid analgesics.	Teens rate the overall riskiness of taking over the counter and opioid analgesics across 6 items. Adapted for ages 12-18. Response options follow those of the NSDUH, with a 4-point Likert scale from 0 (No Risk) to 3 (Great Risk). Participants are asked to rate the risk of taking a previously prescribed opioid for a new condition (medical misuse) and of sharing one’s own prescribed opioid with a friend (non–medical misuse or diversion).	Risk Perceptions – Young Adults	T1, T3

4 STUDY DESIGN

4.1 Overall Design

A. Aims/Hypotheses:

   a. Aim 1. Determine effectiveness of a pre-operative mHealth psychosocial intervention to improve acute pain outcomes in adolescents undergoing major musculoskeletal surgery.

      i. H1: Youth receiving pre-operative CBT (arms 2&4) will have a faster rate of recovery (acute pain intensity and interference: primary outcomes), as well as lower opioid use during the 14 days following hospital discharge, compared to youth who receive pre-operative education (arms 1&3).

   b. Aim 2. Determine effectiveness of a post-operative mHealth psychosocial intervention to improve chronic pain outcomes at 3 months in adolescents undergoing major musculoskeletal surgery.

      i. H2: Youth receiving post-operative CBT only (arm 3) will have lower chronic pain intensity and interference (primary outcomes) compared to youth receiving education control (arm 1).

   c. Aim 3. Determine the combined effects of pre- and post-operative CBT on chronic pain outcomes.

      i. H3: Youth receiving both phases of perioperative CBT (arm 4) will have lower chronic pain intensity and interference (primary outcomes), higher HRQL, as well as lower psychosocial distress, sleep disturbance, and opioid misuse compared to youth receiving single phase intervention or education control at 3 months (arms 1,2,3).

   d. Aim 4. Explore mechanisms of an mHealth psychosocial intervention to prevent CPSP.

      i. H4: Youth receiving combined pre- and post-operative CBT (arm 4) will have lower rates of CPSP compared to arms 1, 2, and 3.

      ii. H5: Reductions in acute postsurgical pain will mediate treatment effects on reducing incidence of CPSP.

      iii. H6: Changes in sleep quality, anxiety and depression, and pain catastrophizing from baseline to 3 months will mediate treatment effect on pain outcomes at 6-months.

B. Phase/Stage of Trial: Phase II

C. Design of Trial

The trial is a randomized controlled effectiveness trial utilizing a 2x2 factorial design. Participants will be randomized immediately after completion of their baseline assessment prior to surgery. Participants will be individually randomized to 1 of 4 conditions that include two treatments (CBT vs. Education) during 2 phases of intervention (pre- and post-surgery phases). Randomization will be stratified by sex (due to female predominance of spine surgery and possible differences in pain outcomes) using block randomization with random block sizes.

After informed consent, study staff will send links for pre-treatment baseline (T1) measures to be completed online prior to randomization. There will be 4 treatment arms. Arm 2 will receive the pre-operative phase of the SurgeryPal intervention, and post-operative education. Arm 3 will receive pre-operative education and the post-operative phase of the SurgeryPal intervention. Arm 4 will receive both pre- and post-operative phases of the SurgeryPal intervention. Arm 1 will receive education control only at both phases and will not receive access to the SurgeryPal intervention.

Participants will self-report all outcomes to reduce risk of bias. All arms will receive standard of care for their surgical procedure; there will be no interaction between the clinical teams at referral sites and the research team. The study investigators and surgery care teams will not know the intervention arm of participants and will not have access to study data until completion of the last participant follow up procedures.

Description of the active treatment condition: The SurgeryPal intervention is a cognitive-behavioral program for youth undergoing major surgery. SurgeryPal is delivered in two 4-week phases: the pre-operative phase, and the post-operative phase. Each phase consists of 3 separate treatment modules for youth and parents, which teach cognitive and behavioral coping skills to target known psychosocial and behavioral risk factors (i.e. anxiety/distress and sleep disturbance) for poorer postsurgical outcomes, and provide training in pain self-management skills. Pre-operative modules include: 1) Preparing for surgery, 2) Coping with stress before surgery, and 3) Getting ready for the hospital. Postoperative modules include: 1) Coping at home after surgery, 2) Return to activities and school, and 3) Long-term recovery. Modules are self-guided and interactive, and focus on phases of preparation and recovery from surgery. The goal of the program is to reduce pain and enhance quality of life following surgery in youth.

Description of control condition: The patient education website will serve as the active comparator. The purpose is to control for time, attention, and online usage. Youth and parents will be provided access to an education website containing information about pediatric surgery at the same time interval as the active intervention; however, there will be no exposure to cognitive and behavioral coping skills. Similar to the CBT condition, the presurgery period of Education will be administered for one month prior to surgery and the postsurgery period will be administered for one month after the post-discharge assessment..

4.2 Scientific Rationale for Study Design

The study design is a multicenter, single-blind (investigator), randomized controlled 2x2 factorial design. Participants are randomly allocated to one of four treatment conditions to test two interventions (CBT and Education) at two phases (presurgery, postsurgery). This design is an efficient way to conduct two trials in one allowing a comparison of the optimal timing of CBT (presurgery vs postsurgery), a comparison between CBT and Education, and whether there are interactive (synergistic) effects of receiving CBT at both presurgery and postsurgery.

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 SurgeryPal intervention teaches six different cognitive and behavioral skills during the pre-operative and post-operative periods focused on anxiety reduction, optimizing sleep, and pain coping skills. Because the intervention is delivered to adolescents via a mobile application the content is standardized. Recognizing the important role that parents/caregivers play in treatment of pediatric pain, the CBT intervention includes a parent website to teach parents how to support their adolescent's use of CBT skills and gives parents skills for reducing their own anxiety. Our prior RCTs using similar technology designs have shown high engagement by parents and youth (over 75% complete all of the intervention). Study data will be analyzed in intention-to-treat analyses regardless of exposure or adherence to the intervention.

4.4 End-of-Study Definition

Once the final enrolled dyad (target: 500) has completed their 6 month post-surgery follow-up assessment (T4), all data collection for the study will be complete.

5 STUDY POPULATION

5.1 Participant Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Teen
    - Willing to comply with all study procedures and be available for the duration of the study
    - 12 to 18 years old at the time of enrollment
    - Undergoing scheduled spinal fusion surgery (eligible indications: juvenile/adolescent idiopathic scoliosis, congenital scoliosis, spondylolisthesis or kyphosis)
- Parent/caregiver
    - Willing to comply with all study procedures and be available for the duration of the study
    - Parent or legal guardian of child who meets study criteria

5.2 Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Teen
    - Does not speak or understand English
    - Has severe learning disability, cognitive impairment or intellectual delay (i.e. unable to read at 5th grade level)
    - Does not have access to a smart device (smartphone, iPad or tablet)
        - Teens can borrow an iPad from the study team if one is available
    - Recent psychiatric admission (in the past 30 days)
    - Seeing counselor for 4+ sessions specifically to prepare for surgery
    - Severe systemic disease (neuromuscular scoliosis, cancer)
    - On a regular treatment regimen for a severe chronic medical condition
    - Prior major surgery (open surgery such as heart, lung, brain, abdominal surgery, or prior spine surgery)
    - Diagnosed chronic musculoskeletal pain condition (complex regional pain syndrome, fibromyalgia or widespread musculoskeletal pain)

- Parent/caregiver
    - Does not speak or understand English
    - Does not have access to a smart device (smartphone, iPad or tablet)

5.3 Screen Failures

Participants who are consented to participate in the study but no longer meet the eligibility criteria prior to randomization will be not be permitted to continue participating in the study, and any data collected from those participants will be excluded. Those participants will not be re-screened.

5.4 Strategies for Recruitment and Retention

1. Our target sample size includes 500 dyads (adolescents ages 12-18 of any sex, race and ethnicity and 1 parent or caregiver, 1000 subjects total), to account for 20% attrition, for a final complete sample of 400 dyads. Based on the percentage of eligible participants in previous studies with similar criteria, we anticipate that we will need to screen 1500 dyads in order to reach our target sample size of 500 dyads.

    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 a geographically diverse range of hospitals and surgery centers across the United States.

        iii. Although we are not enrolling Spanish-speaking participants, we will use Spanish recruitment materials (flyer, one-pager, and website) to target families who may be more comfortable receiving study information in Spanish but could still participate in the study as long as 1 LAR and the teen can read and speak English.

   b. The sample is limited to adolescents between the ages of 12 and 18 years old for two primary reasons: (a) spinal fusion surgeries for idiopathic deformities are most common during this age range and intervention content can be delivered in a similar format across this developmental age range, and (b) youth over the age of 18 years typically undergo surgery at an adult hospital rather than a children's hospital, which would introduce variability in the surgical care if we were to include youth over 18.

2. Participants will be recruited via referral from hospital and surgical centers across the United States. Health care providers will inform patients and families about the study and provide families with study information in the form of a flyer. The flyer will give an overview of the study and provide families with a link/QR code allowing access to a study website which contains more information. Providers will then ask families if they are willing to be contacted by Seattle Children's Hospital (SCH) 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. If families self-refer, the study team may share the patient's first and last initial with the referring site for their records, to prevent duplicate outreach.
3. Additional participants in the United States will be recruited from the community through various organizations associated with pediatric spine surgery, such as the Steel Association/American Spinal Injury Association, Harms Group, Scoliosis Research Society, and Academy of Spinal Cord Injury Professionals, or through their health care providers affiliated with those organizations. The organization or health care provider will share study information with potentially eligible patients via a study flyer or website link. Information will also be shared through SurgeryPal Facebook, Instagram, and Twitter accounts. Interested patients/families may 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.
4. Participants will be individually compensated after each completed study assessment: Each teen and parent will receive a $50 gift card on completion of assessments 1 and 3. The teen will receive a $50 gift card for each completed week of the 2-week T2 daily assessments, and the parent will receive a $50 gift card for completing their T2 assessment. After the final follow-up assessment, the teen will receive a $100 gift card, and the parent a $50 gift card for completion of the study. Each teen and parent participant will receive $20 upon completion of their T2-PT1 survey and upon completion of their T3-PT2 survey. Participants will not receive additional reimbursement for completing the intervention.

5. We will utilize standard procedures for randomized controlled digital health trials 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
        ii. Video conference screening visits will be used to verify legitimacy, screen, and recruit families from the community who are not referred by a known site/provider
    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
    h. Teens without access to a smart device can borrow an iPad from the study team if one is available (only enabled for the use of the SurgeryPal mobile app)
        i. Teens will be asked to sign an agreement to indicate their willingness to borrow an iPad from the study team, take good care of it, notify the study team if it is lost, stolen, or damaged, and return the smartphone at the appropriate time.
    i. The above methods utilized to maximize retention are also applicable for minimizing loss to follow-up and missing data. See section 6.3 for further discussion of loss to follow-up.
6. 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/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 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.

6.2 Participant Discontinuation/Withdrawal from 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), undergo a second major surgery during the study time frame (time points prior to second surgery or new presentation of exclusionary condition will be analyzed), or if their surgery is cancelled.

6.3 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. As noted in Section 5.4, research staff will individually screen completed surveys for missing data and follow up as needed to minimize the amount of missing data.

7 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION

7.1 Study Intervention or Experimental Manipulation Description

There are four intervention conditions. Group 1 will receive education control only and will not receive access to CBT. Group 2 will receive preoperative CBT, and post-operative education. Group 3 will receive pre-operative education and post-operative CBT. Group 4 will receive both pre- and postoperative CBT. The CBT interventions include treatment components modeled after our effective WebMAP program that our team has implemented in multiple populations of youth with painful conditions and their parents (72, 75). The CBT intervention targets stress and anxiety, optimizing sleep duration, and teaching pain self-management skills. The intervention is delivered via a mobile app. A complementary parent intervention delivered via a web program addresses parental anxiety and ways to support youth coping. The goals of the interventions are to improve psychosocial functioning, reduce pain and opioid use, and enhance quality of life following surgery in youth.

The mobile app (SurgeryPal) is an interactive, self-guided intervention. Each module's theme and content is relevant to the timing of the perioperative period (e.g., before surgery, at the hospital, at home), and was developed working closely with patient stakeholders. Pre-surgery intervention includes: 1) Preparing for surgery, 2) Coping with stress before surgery, 3) Getting ready for the hospital. Post-operative intervention includes: 1) Coping at home after surgery, 2) Return to activities and school, 3) Long-term recovery. Treatment duration is 4 weeks for each phase.

The main components of the app include the following: 1) Modules – each consists of several lessons teaching cognitive and behavioral skills, 2) Library - contains (a) Skills delivered via audio and video clips as well as interactive features, with symptom ratings before and after skill practice to provide further feedback to the participant; (b) "For You" articles tailored to surgery timing and symptom ratings; 3) Check in – this is a tracking feature to allow youth to track their pain level, activity, sleep, and mood symptoms on 0-10 NRS through a Daily Check in. These scores generate a customized graph that is updated daily to allow users to track their symptoms and progress. Tailored articles are released to participants in the "For You" section based on their check-in data (e.g. "developing a wind-down routine" article if participant reports poor sleep quality). The same structure and features are available for the pre-surgery CBT program and the post-surgery CBT program.

Education. The patient education website will serve as the active comparator per the group allocation assignment during the pre- and/or post-operative phase(s). The purpose is to control for time, attention, and online usage, and to allow masking to treatment allocation. We are modeling this site after WebEd, an education site that we have constructed for other clinical trials to provide youth and parents with information about chronic pain. Youth and parents will be provided access to a modified version of our education site tailored to content about pediatric surgery. The content does not

include any instruction in the behavioral and cognitive skills taught within the SurgeryPal program. In our prior RCTs using the education control site, parents and youth have shown a high level of engagement and high ratings of treatment credibility (72).

7.2 Administration and/or Dosing

The study intervention will be delivered remotely via the internet/mobile applications. The study intervention consists of two phases of 4 weeks duration: pre-operative and post-operative (starting 3 weeks after surgery). Each treatment phase has 3 modules to be completed by the teen. Each module takes 20-30 minutes to complete or less. One module is released each week at the start of weeks 1, 2, and 3 of the respective treatment phase. A full dose of intervention includes completion of all 3 modules. Daily notifications on the app are used to remind participants to use the intervention and push notifications are used to alert the participants to new content or actions required. Study staff will also maintain close contact with participants during each of the two phases with scheduled text or phone contact occurring at least 2x/week.

An administrative backend database allows a complete record of app usage by each participant. We will record completion of lessons, number of days of app use, number of days of daily monitoring of symptoms, and skills practiced on the app. The education website will monitor logins to the website and number of modules completed so that we will have a record of engagement with the program.

Participants will not interact with one another, nor will they interact with study investigators – all components will be technology-delivered and are self-guided. Participants will interact with research staff for assistance accessing and using the interventions to which they have been assigned.

7.3 Measures to Minimize Bias: Randomization and Masking

After baseline assessment is completed, participants will be block randomized with random block sizes to one of four arms in this 2x2 factorial design, stratified by participant sex. Five-hundred youth will be randomized to 4 treatment arms (see treatment arms table below), therefore we anticipate 125 youth per study group. Group 1 will receive education control only and will not receive access to the SurgeryPal intervention. Group 2 will receive the preoperative phase of the SurgeryPal intervention, and post-operative education. Group 3 will receive pre-operative education and the post-operative phase of the SurgeryPal intervention. Group 4 will receive both pre- and postoperative phases of the SurgeryPal intervention.

Research staff will set up accounts and instruct the participants regarding how to access the assigned intervention. Participants, investigators, and healthcare providers will be masked to treatment assignment.

In our prior RCTs using the education control site, parents and youth have shown a high level of engagement and high ratings of treatment credibility (72). Study coordinators

will be aware of treatment assignment only after completion of the baseline assessment. All assessments will be conducted via automated web-based survey questionnaires thereby eliminating the chance of staff bias affecting results.

Table 7.3.Treatment Arms

Group	Pre-operative	Post-operative
1	ED	ED
2	CBT	ED
3	ED	CBT
4	CBT	CBT

7.4 Study Intervention/Experimental Manipulation Adherence/Fidelity Procedures

Treatment is consistently delivered via the mobile application and 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 mobile application and web programs track each time a parent or youth uses the program and document when lessons are completed. Treatment adherence will be collected by assessing number of days of app use, completion of lessons, number of days of daily monitoring completed, and skills practice. The primary measure of adherence will be the number of lessons completed.

7.5 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 to prepare their teen for surgery, if services were related to a pre-existing problem, and how many sessions their teen had. Although the likelihood of concomitant therapy being received is extremely low, it is important to assess because other therapies and services received may influence the study endpoints independently of the active intervention.

8 STUDY ASSESSMENTS AND PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

We will use a two-stage screening process; first, potentially eligible patients meeting the inclusion criteria will be approached by their providers; if they meet inclusion criteria and are interested in the study they will be referred to SCH staff for follow-up. Providers will refer interested, potentially eligible participants to SCH research team by completing a secure REDCap form including participant and parent names, contact information and an inclusion criteria checklist; SCH study staff will receive email notifications when new REDCap referrals are received and contact the families within 1 business day of receiving the referral. Once referred, SCH staff will discuss the study with families to assess interest and screen for final eligibility according to inclusion and exclusion criteria over the phone 6-12 weeks pre-surgery. Providers and staff at referral sites are not obtaining consent nor participating in any study procedures, and are considered to be not-engaged in research activities. As mentioned in Section 5.4, video conference screening visits will be used to verify legitimacy, screen, and recruit families from the community who are not referred by a known site/provider.

Youth and parents will complete baseline measures prior to randomization. At this time they will also receive a text message confirming their permission to receive study text messages, and an opportunity to opt out of these if desired. Following randomization, youth and parents will complete web/mobile application program modules during the month prior to surgery. Youth will complete daily monitoring of acute recovery during the 14 days at home following hospital discharge using an automated, scheduled daily diary assessment sent via email/text through REDCap. We will briefly check in daily with youth during the days after their surgery to see when they are discharged from the hospital sent via email/text through REDCap. Youth and parents will complete web/mobile application program modules during the month after completion of the 14 day acute recovery monitoring assessment. Pain (pain intensity, pain interference), HRQL, opioid use/misuse, psychosocial distress, and sleep disturbance will be assessed at baseline, 3- and 6- month follow-up. Study questionnaires have all undergone rigorous development and psychometric evaluation, and are appropriate for use in participants in our study age range. Daily monitoring at T2, T3 and T4 takes approximately 2 to 5 minutes to complete each day; T1, T3, and T4 measures take approximately 20-30 minutes.

During participation in the study, there is no interaction between research staff and the clinical providers, who may even be unaware of whether the patient is a study participant. Thus, participants will receive medical pain management per the standard of clinical care such as opioids, or NSAIDs, or physical therapy.

9 ASSESSMENT OF ADVERSE EVENTS AND UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

Clinically related adverse events and unanticipated problems cannot be collected systematically using this study design. This study does not have any study visits, and all outcomes are self-reported by the patient or by the parent. The study team will not have access to clinical data or medical records. Therefore, safety monitoring for this study will be based on three sources, 1) spontaneous reporting of unanticipated problems by parents or youth to study staff, 2) self-reported experiences with the treatments collected systematically using a questionnaire completed by parents and youth at post-treatment time points, and 3) detection of any software or technology problems that compromise patient data.

Standard definitions are described below and will be applied for unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

Definitions

9.1 Unanticipated Problems (UPs)

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.

9.1.2 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.

9.1.3 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.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

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.

9.3.2 Expectedness of SAEs

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.

9.3.3 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

9.4 Overview of safety monitoring for this study

The behavioral intervention being tested in this study has no known risks for adverse events. The study team will have access to three sources of information on unanticipated problems to enable safety monitoring. The first source of information includes spontaneous reporting. Youth or parent participants may spontaneously report unanticipated problems to study staff during the course of routine data collection. This may include reports of adverse events including hospitalization, disability, or death. If this occurs, adverse events will be reported using the procedures described below but will be assumed to be unrelated to the study intervention.

The second source of information is a self-report questionnaire developed for this study to obtain systematic data on the experiences of youth and parents with the behavioral treatments being administered. The questionnaires will be administered at post-treatment time points. This includes the following items,

1. Did you experience any of the following negative effects due to your participation in the study (yes/no for each)?

   a. I couldn't stop thinking or worrying about my pain.

   b. I was overwhelmed by the treatment assignment.

   c. I felt there was more tension at home during treatment.

   d. I was worried thinking if the treatment didn't work, nothing would work.

   e. I was anxious because of the things I was asked to do.

2. How much discomfort did these experiences cause? 0 ('Did not affect me at all") to 3 ("Affected me very negatively").

3. During this study, did you experience any stressful life event unrelated to your participation in the study (for example: a car accident, an illness in the family, a break up, the loss of a pet)? (yes/no)

a. If yes, tell us a little about what happened (open text field).

Study staff at SCH will follow up by phone with any participants who endorse experiencing a great deal of discomfort (i.e., ratings of 3, affected me very negatively) from study participation to find out more information and identify any adverse events.

The third source of information is detection of any software or technology problems that compromise patient data. UPs can occur if the data system is breached, confidentiality is not maintained, or study data is not recorded and is lost.

At the time of DSMB evaluations, unanticipated problems from these three sources will be tabulated by intervention arm and included in the closed DSMB report.

9.5 Reporting Procedures

9.5.1 Unanticipated Problem Reporting to IRB, NICHD and the Medical Monitor at NCATS

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form by the Co-PIs. The report will include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;

- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, NICHD and NCATS within 5 business days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, NICHD and NCATS within 5 business days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

9.5.2 Report of death

Death during the study will be reported using the SAE report form of the Data Coordinating Center to the IRB, NICHD and NCATS within 7 days of the investigator becoming aware of the death.

10 STUDY OVERSIGHT

Study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in appropriate clinical, statistical, scientific and ethical disciplines. The DSMB will meet before study enrollment begins and every six months thereafter, until the end of the study; to approve the study protocol prior to implementation; to assess participant safety; to monitor accrual of study participants; and to oversee study progress and data integrity for the study.

The DSMB will operate under the rules of a charter that will be approved at the DSMB organizational meeting. The DSMB will provide recommendations to the funding agency regarding proceeding with the study as planned, proceeding with modifications, or terminating the study. The DSMB will provide recommendations to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) as noted in the DSMB Charter.

This study may be suspended or prematurely terminated if, in the opinion of the investigators or the NICHD, there is reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. The investigators will promptly inform the IRB, providing the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

11 STUDY MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Clinical site monitoring and remote monitoring for this study will be performed by the Duke/Vanderbilt (Clinical Coordinating Center or CCC) and Utah (Data Coordinating Center or DCC) Trial Innovation Centers, respectively. Duke, Vanderbilt and Utah will not administer research procedures or interventions.

11.1 Clinical Site Monitoring

The Data Coordinating Center (DCC) utilizes risk-based methodology to identify and correct problems that may arise. Since all study data are self-reported by participants and parents, monitoring will be focused on assurance of proper consenting and assenting procedures, maintenance of IRB approval, and security of databases maintained at Seattle Children's Hospital. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, NIH and NIH Program staff. The NIH reserves the right to conduct independent clinical site monitoring as necessary.

11.2 Remote Monitoring

As the study data are self-reported by participants and parents, there is no source verification of data, and remote monitoring will be primarily focused on assurance that implementation of the intervention matches the intervention assigned by randomization.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical Hypotheses

1. H1: efficacy
    a. H1 null: Youth receiving pre-operative CBT (arms 2&4) will have equal rates of recovery (acute pain intensity and interference: primary outcomes), as well as equal opioid use during the 14 days following hospital discharge, compared to youth who receive pre-operative education (arms 1&3).
    b. H1 alternative: Youth receiving pre-operative CBT (arms 2&4) will have faster rates of recovery (acute pain intensity and interference: primary outcomes), as well as lower opioid use during the 14 days following hospital discharge, compared to youth who receive pre-operative education (arms 1&3).
2. H2: efficacy
    a. H2 null: Youth receiving post-operative CBT only (arm 3) will have equal chronic pain intensity and interference (primary outcomes) compared to youth receiving education control (arm 1).
    b. H2 alternative: Youth receiving post-operative CBT only (arm 3) will have lower chronic pain intensity and interference (primary outcomes) compared to youth receiving education control (arm 1).
3. H3: efficacy
    a. H3 null: Youth receiving both phases of peri-operative CBT (arm 4) will have equal chronic pain intensity and interference (primary outcomes), as well as equivalent HRQL, psychosocial distress, sleep disturbance, and opioid misuse compared to youth receiving single phase intervention or education control at 3 months (arms 1,2,3).
    b. H3 alternative: Youth receiving both phases of peri-operative CBT (arm 4) will have lower chronic pain intensity and interference (primary outcomes), as well as higher HRQL, lower psychosocial distress, sleep disturbance, and opioid misuse compared to youth receiving single phase intervention or education control at 3 months (arms 1,2,3).

12.2 Sample Size Determination

Data available from our preliminary perioperative and chronic pain studies (Rabbitts, Groenewald et al. 2015, Rabbitts, Zhou et al. 2015) and from prior perioperative intervention studies (LaMontagne, Hepworth et al. 2003, Charette, Fiola et al. 2015, Davidson, Snow et al. 2016) allowed us to conduct power calculations on primary pain outcomes for each of our aims (see below).

Power/sample size calculations for Aims 1-4.

Aim	Comparison Groups*		Primary Outcome variables	Mean difference (SD)	Power	N per smallest comparison group
	Control	Intervention				
1	Pre-operative education (Arms 1&3, n =200)	Pre-operative mHealth (Arms 2&4, n= 200)	Brief Pain Inventory; T2	0.43 (0.38) 0.32 (0.38)	80% 90% 80% 90%	14 18 24 31
2	Education control alone (Arm 1, n = 100)	Post-operative mHealth (Arm 3, n = 100)	Brief Pain Inventory; T3	0.9 (1.7)	80% 90%	18 30
3	Single phase mHealth or education control alone (Arms 1,2,3, n =300)	Pre- & post-operative mHealth (Arm 4, n = 100)	Brief Pain Inventory; T3	1.0 (1.8)	80% 90%	35 46
4	Single phase mHealth or education control alone (Arms 1,2,3, n = 300)	Pre- & post-operative mHealth (Arm 4, n = 100)	Rate of CPSP (defined by NRS and PedsQL; T3)	15%	80% 90%	86 113

*The number of treatment arms in the smallest comparison group differ for each aim; total available n per analysis is listed based on a final complete sample of 400 youth.

For Aim 1, the primary parameter of interest is the rate of recovery modeled using an exponential decay model. Based on our pilot data, we assume we will be seeing log(rate)=-1.21 (SE=0.38) in the intervention arm, which translates into a half-life (days taken to achieve 50% reduction in BPI outcome from time 0) of 4.13 days. If the control has a 50% increased half-life (then log(rate)=-1.64) then a sample size 18 subjects per arm would provide 90% power to detect the difference (SD=0.38); N=14/arm for 80% power. If we assume the control arm will double the half-life (takes twice as long to achieve the same amount of reduction) which has log(rate)=-1.93, then sample size of 7/arm and 6/arm are needed for 90% and 80% power. Using a more conservative estimate of 35% increased half-life of recovery in the control arm, 31 subjects per arm would provide 90% power; N=24/arm for 80% power.

Based on our power calculations (provided in above table), a final sample size of 400 youth (100 per arm) will allow sufficient sample size in each comparison group to provide ample power to test each hypothesis on primary outcomes (Aims 1-3). For exploratory outcomes (Aim 4), we anticipate a rate of CPSP of 31% (see preliminary studies). With a sample size of 400 (i.e. 100 in smallest comparison group), we will have >80% power to detect an absolute reduction of 15% in the rate of CPSP in the group receiving combined full pre- and post-operative intervention.

Although we have had >95% retention in our prior perioperative and mHealth intervention studies, we conservatively plan for 20% attrition, and therefore plan to enroll 500 dyads for a complete sample of 400 dyads, which will allow us to test the primary study hypotheses with optimal power.

12.3 Populations for Analyses

Our main analyses will be intent-to-treat; children are the unit of analysis. All randomized participants will be included in analyses.

12.4 Statistical Analyses

12.4.1 General Approach

Our main analyses will be intent-to-treat analyses which will include all participants randomized, regardless of intervention compliance, though additional sensitivity analyses will be performed to examine the effect of compliance. Given that youth are individually randomized and receive individual treatment, children are the unit of analysis for the sample size calculations and proposed data analysis plan. If strong correlations exist within participants for repeated measures or among participants from the same study site, they will be accounted for using participant- and/or site- specific random effects in mixed effects models. Randomization at the participant level with stratification by participant sex should balance many observed and unobserved confounders. Per the CONSORT 2010 Statement, we will not test for baseline differences between intervention and control groups as part of analysis (Schulz, Altman et al. 2010). We have *a priori* identified child/family socio-demographics (e.g., age, sex, race/ethnicity), strong prognostic factors (pre-surgery pain severity), and study site as covariates for the proposed outcomes and will adjust for them in our analyses. For the primary aims we will perform cross-sectional analysis focusing on 2 weeks post discharge (acute pain) and 3-months postsurgery (chronic pain) to evaluate both the immediate and short term effects of the interventions. We will conduct analyses to test for differences in effect among sex, racial, and/or ethnic groups as outlined below. In secondary data analysis we will perform longer-term data analysis examining outcomes over 6 months follow up.

12.4.2 Analysis of the Primary Endpoint(s)

Primary analytic plan for Hypothesis 1 Primary Outcomes. *Youth receiving pre-operative CBT (arms 2 and 4) will have lower pain intensity and interference (primary outcomes) during the 14 days following hospital discharge, compared to youth who receive pre-operative education (arms 1 and 3).* The primary outcomes will be the individual rate of recovery over 14 days in pain intensity and interference (**Brief Pain Inventory**) assessed immediately post-discharge. For this hypothesis, arms 1&3 will be combined into the control group (pre-operative education); arms 2&4 will be combined into the intervention group (receiving pre-operative mHealth intervention). Note these outcomes will be assessed before any post-operative mHealth intervention has taken place.

To test the hypothesis that intervention youth would have a more rapid rate of recovery in pain and interference than control youth, we will model a trajectory of pain symptoms using an exponential decay framework. Given that pain will be assessed 14 times, we believe the data will provide sufficient resolution to model time as a continuous variable

when examining change in pain intensity and interference over time. Let Y_{ij} denotes the BPI measured for *i*th subject at time t_j, x_i denotes the group assignment for *i*th subject, $\boldsymbol{Z}_i$ denote the vector of covariates, we will consider the following general model specification: (1) $Y_{ij} = f\left(\boldsymbol{\beta}_i^{(x_i)}, t_j\right) + \boldsymbol{\gamma Z}_i + \epsilon_{ij}$; $\boldsymbol{\beta}_i^{(x_i)} \sim N\left(\boldsymbol{b}^{(x_i)}, \boldsymbol{\Sigma}\right)$; $\epsilon_{ij} \sim N(0, \sigma^2)$. Function $f(\boldsymbol{\beta}, t)$ can take flexible functional forms to capture different shapes of trajectories. For example, $f(\boldsymbol{\beta}, t) = \beta_0 + \beta_1 t$ represents a linear trend over time; $f(\boldsymbol{\beta}, t) = \beta_0 + \beta_1 t + \beta_2 t^2$ represents a quadratic trend over time; or more generally, we can assume a restricted cubic spline for $f(\boldsymbol{\beta}, t)$ to represent more flexible trajectory shapes. Based on our pilot study and prior studies in the literature, we have observed that pain symptoms and other health outcomes exhibit faster rates of improvement in the acute phase (<1 month), and then changes tend to slow down and level off. For these reasons a more parsimonious and accurate function for time trend could be exponential decay function in the form $f(\boldsymbol{\beta}, t) = \beta_2 + (\beta_0 - \beta_2) \times \exp(-\beta_1 t)$, where *t* is time, β_0 is the initial value at *t=0*, β_2 is the asymptote as *t* goes to infinity, β_1, ***constrained to be positive***, is the rate of change or how quickly the process decays/improves from the initial value to the asymptote.[147] Examples of trajectories based on exponential decay functions are shown in Figure 6. Parameters ${\beta_1}^{(1)}$ and ${\beta_1}^{(2)}$ are the group specific shape parameters, and equality of these parameters will be tested using multivariate Wald-test to assess the hypothesis that pain (BPI) declines more quickly in mHealth intervention subjects compared to control. Note the rate of change β_1 could also be influenced by other biopsychosocial variables and clinical factors, we can address this by considering a more advanced hierarchical model in which: (2) $\log\left(\beta_1(x_i, \boldsymbol{Z}_i)\right) = \alpha_0 + \alpha_1 x_i + \boldsymbol{\alpha}_2 \boldsymbol{Z}_i$, the logarithmic transformation ensures positivity of the change rate and parameter $\alpha_1$captures the difference in rate of change between study arms when $x_i$is the study arm indicator for *i*th subject..

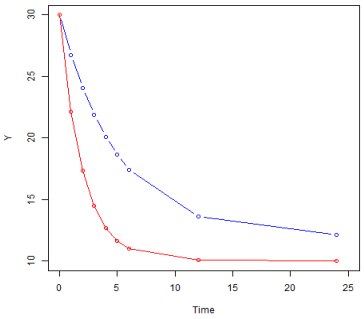


Figure 6: Examples of trajectories based on an exponential decay function

Primary analytic plan for Hypothesis 2 Primary Outcomes. *Youth receiving post-operative CBT alone (arm 3) will have lower pain intensity and interference (primary outcomes), compared to youth receiving education control (arm 1).* The primary outcomes will be the average of 7 days of daily pain intensity and interference (**Brief Pain Inventory**) assessed at 3 months postsurgery. We will consider the education control arm (arm 1) as the control group and post-operative mHealth alone arm (arm 3) as the intervention group. Note both of these groups receive pre-operative education control. The main analysis will be based on covariates adjusted linear regression models. We will consider pain outcomes as continuous outcomes and apply linear regression models. Specifically, let y_i denote the outcome for participant *i*, let U_i be the intervention indicator (0=control, 1=intervention), let $\boldsymbol{X}_i$ be the collection of covariates specified a priori, then the regression equations will take the following form $y_i = b_0 + U_i\alpha + \boldsymbol{X}_i\beta + \epsilon_i$, (1) . The

parameter of interest (α) captures the expected difference between intervention and control groups and will be tested for significance based on Wald t-test.

Primary analytic plan for Hypothesis 3 Primary Outcomes. *Youth receiving both phases of peri-operative CBT (arm 4) will have lower pain intensity and interference compared to youth receiving single phase intervention (arms 2 and 3) or education control alone (arm 1) at 3 months.* The primary outcomes will be the average of 7 days of daily pain intensity and interference (**Brief Pain Inventory**) assessed at 3 months postsurgery. For this hypothesis comparing individual study arms, the predictor of interest U_i in the regression equation (1) will be treated as a 4-category factor (0=arm #4 both pre- and post-operative mHealth interventions, 1=arm #1 education control, 2= arm #2 pre-operative mHealth, 3= arm #3 post-operative mHealth). Using arm #4 as the reference group, the coefficients α estimate the expected differences between arms #1-3 versus arm #4 and will address our hypothesis. Note using proper contrast and linear combination of regression coefficients, Hypothesis 2 can be addressed by this regression model as well.

12.4.3 Analysis of the Secondary Endpoint(s)

Primary analytic plan for Hypothesis 1 Secondary Acute Outcomes. *Youth receiving pre-operative CBT (arms 2 and 4) will have lower opioid use during the 14 days following hospital discharge, compared to youth who receive pre-operative education (arms 1 and 3).* For this hypothesis, arms 1&3 will be combined into the control group (pre-operative education); arms 2&4 will be combined into the intervention group (receiving pre-operative mHealth intervention). Secondary outcomes at Acute phase include opioid use (**Brief Pain Inventory Short Form**; # days of opioid use during 14 days daily monitoring). Note these outcomes will be assessed before any post-operative mHealth intervention has taken place. Our primary analysis will be based on covariates adjusted regression models. Opioid days will be treated as count variables and analyzed using Poisson regression. Specifically, let y_i denote the outcome for participant *i*, let U_i be the intervention indicator (0=control, 1=intervention), let $\boldsymbol{X}_i$ be the collection of covariates specified a priori, then the regression equations will take the following form

$$y_i = b_0 + U_i\alpha + \boldsymbol{X}_i\beta + \epsilon_i, \qquad (1)\ .$$

The parameter of interest is α which captures the expected difference between intervention and control groups and will be tested for significance based on Wald t-test.

Primary analytic plan for Hypothesis 3 Secondary Chronic Outcomes. *Youth receiving both phases of peri-operative CBT (arm 4) will have lower pain intensity and higher HRQL, as well as lower pain interference, psychosocial distress, sleep disturbance, and opioid misuse compared to youth receiving single phase intervention (arms 2 and 3) or education control alone (arm 1) at 3 months.* For this hypothesis comparing individual

study arms, the predictor of interest U_i in the regression equation (1) will be treated as a 4-category factor (0=arm #4 both pre- and post-operative mHealth interventions, 1=arm #1 education control, 2= arm #2 pre-operative mHealth, 3= arm #3 post-operative mHealth). Secondary Outcomes include HRQL (**PedsQL**), psychosocial distress (**Pain catastrophizing- parent and child; PROMIS Anxiety and Depression Instruments- child**), sleep disturbance (**ASWS**), and opioid misuse (**NIDA Modified ASSIST Tool**) assessed at 3 months postsurgery. Using arm #4 as the reference group, the coefficients α estimate the expected differences between arms #1-3 versus arm #4 and will address our hypothesis. Note using proper contrast and linear combination of regression coefficients, Hypothesis 2 can be addressed by this regression model as well.

12.4.4 Descriptive Statistics

Per the CONSORT 2010 Statement, we will not test for baseline differences between intervention and control groups as part of analysis (Schulz, Altman et al. 2010). We have *a priori* identified child/family socio-demographics (e.g., age, sex, race/ethnicity), strong prognostic factors (pre-surgery pain severity), as covariates for the proposed outcomes and will adjust for them in our analyses.

We will summarize acute phase primary outcomes (**Brief Pain Inventory Short Form**; pain intensity and pain interference during the 14 days after discharge from surgery) and other outcomes (**Brief Pain Inventory Short Form**; # days of opioid use during 14 days daily monitoring) using descriptive statistics. Arms 1&3 will be combined into the control group (pre-operative education); arms 2&4 will be combined into the intervention group (receiving pre-operative mHealth intervention). Note these outcomes will be assessed before any post-operative mHealth intervention has taken place.

Chronic phase outcomes including pain severity (**Brief Pain Inventory**), HRQL (**PedsQL**), psychosocial distress (**Pain catastrophizing- child and parent; PROMIS Anxiety and Depression Instruments- child**), sleep disturbance (**ASWS, and CRSP sleep duration**), and opioid misuse (**NIDA Modified ASSIST Tool**) assessed at 3 months postsurgery, will be compared between individual treatment arms. Similar to what we outlined above for acute outcomes, we will summarize these outcomes using descriptive statistics.

12.4.5 Sub-Group Analyses

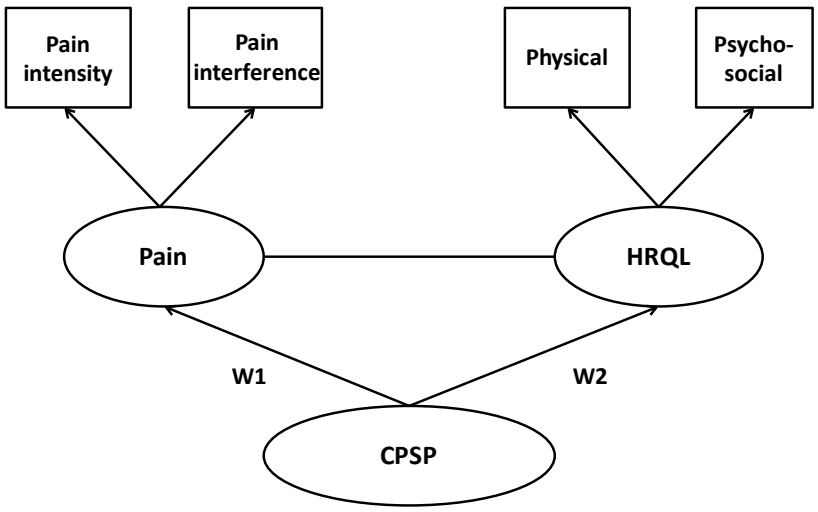
See Exploratory Analyses below: Analyses to test for differences in effect among sex, racial, and/or ethnic groups.

12.4.6 Tabulation of Individual Participant Data

Individual participant data will not be listed.

12.4.7 Exploratory Analyses

Primary analytic plan for Hypothesis 4 (exploratory). *Youth receiving combined pre- and post-operative CBT (arm 4) will have lower rates of CPSP (outcome: moderate-severe pain with impairment in HRQL) at 3- and 6-months compared to arms 1, 2, and 3.* A binary outcome chronic post-surgical pain (CPSP) will be defined based on pain intensity (**Pain Intensity**), and HRQL (**PedsQL**) at 3-months post-surgery. We will develop and test cut points for chronic postsurgery pain (CPSP) by considering both pain severity and health related quality of life (both treated as latent constructs). Toward this we will conduct latent class analysis (LCA) following the proposed framework (see figure). This model will be implemented using multilevel structural equation models (SEM) (Bollen and Curran, 2006, Little, 2013, Preacher, Wichman et al., 2008). The parameters of interest are coefficients linking latent constructs "Pain" and "HRQL" (W1 and W2) to latent construct "CPSP" as the weighted sum will identify CPSP based on pooled information. We will conduct cross-validation using part of the data to develop the weights and part of the data to validate the predictive performance. Our evaluation of intervention effects on CPSP will then be based on the cut points derived from above analysis. It will be analyzed using a logistic regression model and the model will be specified similar to what is outlined for Hypothesis 3.



To test Hypothesis 5 (exploratory), *Reductions in acute postoperative pain will mediate treatment effects on reducing incidence of CPSP*, we will conduct exploratory mediation analysis. We will assess the extent through which acute post-operative pain intensity and interference exert their influence on (i.e., mediate) change in pain intensity, HRQL, and pain interference at 3 months follow up via the intervention. The mediational effects of acute pain reduction will be assessed using two comparison groups: education control only (Group 1) versus pre-operative mHealth intervention only group (Group 2), so that any mediation effect will not be confounded by second phase intervention. We will use a structural equation modeling (SEM) approach: specifically, we will evaluate

mediation by decomposing a total effect of intervention on the pain (**Brief Pain Inventory; Pain Intensity**) and HRQL (**PedsQL**) outcomes into direct effects and indirect effects (MacKinnon, Lockwood et al. 2002, MacKinnon 2008, Mackinnon and Fairchild 2009). The indirect effects represent the influence of the intervention on change in chronic pain and HRQL via changes in acute post-op pain severity (**Brief Pain Inventory Short Form**). From a set of 5,000 bootstrap samples, 95% bias-corrected confidence intervals will be calculated for the indirect effects. A significant indirect effect will indicate that the pre-surgery intervention influences change in pain severity and interference at 3 months (short term chronic pain endpoint) by influencing acute post-op pain severity and interference. In addition, we will conduct exploratory mediation analysis by including all 4 study arms. Next we will extend this mediation analysis by considering "moderated mediation" through adding the interactions between second phase intervention and short term acute pain reduction in the mediation equations.

To test Hypothesis 6 (exploratory), We will assess the extent through which psychosocial factors exert their influence on (i.e., mediate) changes in pain severity and pain interference during post-surgery recovery via the intervention. We will use a structural equation modeling (SEM) approach (Brown 1997, Little, Card, et al. 2007). Specifically, we will evaluate mediation by decomposing a total effect on the pain outcome slope into direct effects and indirect effects. The indirect effects represent the influence of the intervention on change in pain outcomes via psychosocial factors. From a set of 5,000 bootstrap samples, 95% bias-corrected confidence intervals will be calculated for the indirect effects (Efron 1987, MacKinnon, Lockwood, et al. 2004, Shrout and Bogler 2002, Little 2013). A significant indirect effect will indicate that the intervention affects change in pain outcomes by influencing psychosocial factors. When appropriate, multi-level structural equation modeling (MSEM) will estimate predictive relationships while handling nested interdependence among observations (Little 2013). Using a SEM approach, we will conduct exploratory mediation analyses of sleep quality, anxiety and depression, and pain catastrophizing as mediators of the relationship between intervention and change in pain outcomes.

Analyses to test for differences in effect among sex, racial, and/or ethnic groups. We will conduct moderation analysis to examine whether there are differential intervention effects across sex, racial, and ethnic groups on primary and secondary acute (Aim 1) and chronic (Aims 2 and 3) outcomes. These data are self-reported on the **Demographic Form.** The effect modifications will be examined by including group-by-moderator interaction terms in regression Equation (1). Moderation effects will then be tested by assessing the significance of the proper contrast among corresponding regression coefficients. Overall moderation can be assessed with likelihood ratio test (LRT) and F-statistic, and multivariate Wald-type t-statistic comparing models with and without interactions. We will also conduct additional subgroup analysis within groups defined by moderators to examine the differential effect sizes within individual subgroups.

Secondary data analysis.

We will perform additional longitudinal data analysis to examine change in pain intensity and pain interference over time. Pain intensity and pain interference outcomes assessed at baseline, 2-weeks, 3-months and 6-months will be modelled using linear mixed effects regression models. Predictors will include time indicator, study arm indicator, arm-by-time interaction term and *a priori* identified covariates. The arm-by-time interaction coefficients will assess differential changes in outcomes from baseline to post-op assessments between study arms thus will be parameters of interest. Participant-specific random effect will be included in the model to account for within participant correlations due to repeated measures. Estimation will be based on restricted maximum likelihood (REML) and significance will be assessed using likelihood ratio test (LRT) comparing models with and without interactions (Fitzmaurice and Laird, 2011, Pinheiro and Bates, 2000, Stroup, 2012).

Additional moderation analysis will also be conducted. Specifically, we will examine whether participant age, baseline adolescent sleep quality (**ASWS)**, and baseline psychosocial distress (**Pain catastrophizing- child and parent, PROMIS Anxiety and Depression Instruments- child, PHQ-4- parent**) strengthen or weaken the impact of the intervention on change in child pain intensity and pain interference. This will be achieved by including group-by-moderator interaction terms in Equation (1). Moderation effects will then be tested by assessing the significance of the contrast among corresponding regression coefficients. Overall moderation can be assessed with multivariate Wald statistic and F-test based on analysis of variance (ANOVA) for nested models. We will also conduct additional subgroup analysis within groups defined by moderators to examine effect modifications.

Missing Data

The primary analyses will be based on all available data.

Amount of missing data and pattern of missing data will be examined. At each time point (T2-T4), we will examine the extent of missing data, such as the number of days completed by each study participant and the distribution of the number of days of missing data as well as the pattern of missingness: whether the missing data only occurs in the early vs later portion of each data collection time point or whether it is random. Simple imputation using the “best” and “worst” scenarios for missing data will help identify the influence of missing data on the study results. If a substantial amount of missing data exists, in addition to our primary data analysis using all available data, we will conduct additional sensitivity analysis using multiple imputations with changed equations (MICE), assuming missing at random. Missing values are imputed based on the observed values for a given individual and the relations observed in the data for other participants, assuming the observed variables are included in the imputation

model. Multiple imputation procedures, particularly MICE, are very flexible and can be used in a broad range of settings. Because multiple imputation involves creating multiple predictions for each missing value, the analyses of multiply imputed data take into account the uncertainty in the imputations and yield accurate standard errors. The MICE approach is a flexible yet powerful technique to address missing data issues and has demonstrated excellent performance in practice (Molenberghs and Kenward, 2007, Collins, Schafer et al. 2001, van Buuren 2007, Little, D'Agostino et al. 2012). If missing not at random is suspected based on the examination of the missing data, the pattern mixture model will be used to estimate model parameters for different patterns of missing data and then combine the estimates over strata (Little 2012).

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain research records for this study, in compliance with ICH E6 and regulatory/institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives of the Data and Clinical Coordinating Centers (DCC & CCC), upon request, for source verification of study documentation (protocols, measures, and recruitment materials), quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. In addition, medical information and data generated by this study must be available for inspection upon request by representatives NIH and the Institutional Review Board (IRB) for each study site.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The REDCap database for participant and parent reported surveys and diaries will be implemented at the University of Utah based on specifications from the study investigators and Seattle Children's research staff. The database will be tested by the DCC clinical data managers and statisticians, and will be reviewed by the study investigators compared to the original specifications to assure that the database has been constructed appropriately. All DCC and Seattle Children's research staff and investigators will have completed human subjects research and GCP training, and will receive individual training on the trial protocol and the database systems.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

This trial will use the IRB at the main site, Seattle Children's Hospital. Referring sites are not engaged in human subjects research unless otherwise specified by their local IRB policies. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the SCH IRB for review and approval. Approval of both the protocol and the consent form(s) will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A combined consent (18 years) and assent (12-17 years) form describing in detail the study procedures and risks will be given to interested adolescents and caregivers (electronically, via PDF). Consent forms will be IRB-approved, and the adolescent and parent are required to read and review the document or discuss the document in detail with a research staff member. The research staff member will explain the research study to the participant and answer any questions that may arise. The staff member will then go through a consent conversation where they will ask the adolescent and caregiver a series of questions designed to ensure that potential participants understand the voluntary nature of the study, the consent/assent process, study procedures, what they will be asked to do, and the potential benefits/risks. At the end of the consent conversation, if the adolescent and caregiver are still willing to participate, research staff will obtain verbal consent from the parent and consent/assent from the teen depending on age. The adolescent and caregiver will then sign the electronic informed consent/assent document (using the REDCap e-consent framework) prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their family members or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. Participants may download an electronic copy of the signed informed consent document for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study; this study is purely adjunctive and will not affect

or change their clinical care. The consent process will be documented in the research tracking database.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

The study population includes children ages 12-18 years. Pediatric studies are particularly necessary to document effectiveness of psychosocial pain management interventions as the developmental appropriateness of adult interventions cannot be assumed. Individuals of any gender or racial/ethnic group may participate.

15.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. No identifiable data will be published or disseminated outside Seattle Children's Hospital or the DCC at the University of Utah.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (*https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

NIH Data Sharing Policies

As described in section 17, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Not applicable. Neither specimens nor identifiable data will be banked for future research.

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for maintaining records of screening and consenting participants in this study (these records will be stored locally at Seattle Children's and through REDCap, hosted by UW ITHS). Study data, stored at University of Utah, are self-reported by participants and parents, and these data are not subject to discrepancy management or DCC follow up and correction.

16.1 Data Management Responsibilities

Data will be produced by participants and parents. Study staff are responsible to train participants so that valid data entry is accomplished. Data will be stored at the University of Utah, which is responsible for security of the information systems.

16.2 Data Capture Methods

Participant and parent questionnaires will be entered into the study REDCap data base via secure encrypted Internet connection. Usage information from the intervention backend server will be captured from the phone application. No PHI is collected or stored in the phone application or website.

16.3 Types of Data

Two primary types of data will be collected –questionnaire responses for patient-report outcome measures collected via REDCap (surveys and daily diaries) and treatment adherence/engagement data (derived from app analytics).

16.4 Schedule and Content of Reports

Participant accrual and scheduled assessments will be tracked by Seattle Children's research staff to facilitate encouraging completion of procedures by participants. These data, as well as participant questions described in Section 9, will be incorporated into DSMB reports. These reports will be prepared and submitted to the DSMB as described in the DSMB charter. Study progress reports will be delivered on a monthly basis to investigators and staff at referring sites to encourage participant referral.

16.5 Study Records Retention

Study records will be maintained at the University of Utah for at least three years from the date that the last grant federal financial report (FFR) is submitted to the NIH. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)]. After study completion, Seattle Children's hospital will maintain an identifiable dataset for at least seven years.

16.6 Protocol Deviations

Study data are self-reported by participants and parents, and missing data will not be considered protocol deviations since participant behavior is out of the control of the study investigators and research staff. The primary protocol deviation that will be of importance in this study is if a participant is randomized to an intervention arm, but receives the wrong intervention. For example, if the participant has been randomized to only receive the educational website both pre and post-surgery, but is provided with the active CBT application, this is a protocol deviation that must be reported to the DCC. Such a deviation will require corrective actions to be developed and implemented to prevent recurrence. Protocol deviations will be part of the report provided to the DSMB.

17 PUBLICATION/DATA SHARING

This study will comply with all applicable NIH Data Sharing Policies. See *https://grants.nih.gov/policy/sharing.htm* for policies and resources.

NIH Public Access Policy

The NIH *Public Access Policy* requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to *PubMed Central* immediately upon acceptance for publication. This ensures that the public has access to the published results of NIH funded research.

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

The study is a clinical trial and will comply with the NIH policy that establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results of these trials are submitted to ClinicalTrials.gov.

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19 SUPPLEMENTAL MATERIALS

These documents will be submitted to the IRB as separate files.