PROJECT TITLE:

Web-MAP for children with chronic pancreatitis (WebMAP- CP)

PRINCIPAL INVESTIGATOR:

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Contents

1. Objectives

1.1. Purpose, specific aims, or objectives:

This project will deliver a first ever randomized, double-blinded and placebo controlled nonpharmacological pain intervention to children with CP/ARP and potentially identify patient-specific biological and psychosocial factors associated with favorable versus poor responsiveness to CBT to enable precision medicine approaches, consistent with priorities of the Federal Pain Research Strategy.

Aim 1. To determine the efficacy of web-based CBT in children with CP/ARP.

Aim 2. To identify the genetic co-variants associated with treatment response to web-based CBT.

Aim 3. To identify clinical and psychosocial factors associated with treatment benefit from web-based CBT.

1.2. Hypotheses to be tested:

Hypothesis 1: Children receiving CBT will have greater reductions in pain-related disability (primary outcome), pain, anxiety and depressive symptoms, opioid use, and HRQOL (secondary outcomes) compared to the education control group. To test this hypothesis, we will conduct a randomized and double-blinded controlled trial of web-based CBT (WebMAP) vs education (WebED). We will evaluate changes in pain, HRQOL, emotional functioning, medication use, health care utilization at baseline, 2 months, and 6 months.

Hypothesis 2: Genetic co-variants associated with pancreatitis, inflammation, lipid and drug metabolism will predict response to therapy. To test this hypothesis, we will evaluate targeted next generation sequencing of genes involved in pancreatitis risk (CASR, CFTR, CTRC, SBDS, SBDSP – pseudogene, SPINK1, CEL, CELP – pseudogene, CPA1, CLDN1 (key SNPs), PRSS1, PRSS2, PRSS3, PRSS1-2 locus, GGT1 and UBR1)), lipid metabolism (APOA5, APOC2, FABP, LPL), inflammation (IL10, IL22, IL22RA1,
IL22RA2, IL23R) and drug metabolism (COMT, HTR2A, CYP2C19, CYP2D6,
CYP3A4, CYP3A5, OPRD1 and OPRM1) in children with CP/ARP who undergo WebMAP vs WebED. Risk stratification analysis will be done to identify genotypic factors that will predict response to treatment.

Hypothesis 3: Baseline clinical characteristics (i.e. demographics, age at diagnosis, abdominal pain frequency and severity, number of pancreatitis attacks, imaging findings), and baseline emotional and family functioning will predict pain and health outcomes at 6 months.

2. Background

2.1. Relevant prior experience and gaps in current knowledge:

Current state of the science: pediatric pain self-management interventions. Psychological treatments for pediatric chronic pain have included predominantly cognitive-behavioral therapy (CBT) self-management interventions such as pain education, relaxation training, cognitive skills, behavioral activation, and relapse prevention. Psychological therapies are effective in reducing pain intensity and pain-related disability of children and adolescents with chronic pain, including abdominal pain 15. To date, there are no established pediatric pain self-management interventions for pediatric CP/ARP.

Challenges to provide pain self-management interventions. Despite the effectiveness of pain self-management programs, many barriers prevent children from receiving self-management for chronic pain: i) children/caregivers may be reluctant to seek out mental health services for pain management, ii) access may be limited due to geographic restrictions (e.g., available only in tertiary centers), iii) small number of trained clinicians are available to deliver the therapies, iv) families often experience burden in taking time off school and work, and v) direct and indirect costs of therapy visits are often prohibitive. Highly trained personnel deliver

these therapies in individual or group sessions in specialty clinics; therefore, services are not widely available for community and home-based settings. These barriers have led our group to develop a highly successful and well-accepted childhood pain self-management intervention delivered via Internet.

Rationale for web and mobile technologies to enhance delivery of pain self-management care for pediatric CP/ARP. We took advantage of information and communication technology to expand opportunities for intervening with families remotely, thus greatly extending the reach of clinical services for pain self-management. There is now strong evidence for internet-delivered chronic pain self-management interventions in both adult and pediatric populations 16 with improvement in pain and disability. In addition to improving access, these technologies empower youth to take an active role in managing their condition by providing "in the moment" access to pain coping strategies.

2.2. Relevant preliminary data:[1]

Evaluation of Web-Based Management of Adolescent Pain (WebMAP). Dr. Palermo developed an Internet delivered CBT pain intervention called WebMAP that includes 8-10 weeks of online modules to teach relaxation skills, pain coping strategies, and parent behavioral and communication techniques to youth with mixed chronic pain conditions. In the initial RCT with 48 youth (11–17 years) with a variety of pain conditions (e.g., headache, stomachache, musculoskeletal pain), significant reductions in pain and disability were found for youth receiving WebMAP compared to a wait-list control group.51 Following up on this initial trial, Dr. Palermo recently completed a second large multicenter RCT of WebMAP involving 273 adolescents (ages 11-17 years) with chronic pain and their parents from 14 centers in the U.S. and Canada 23. Adjunctive to treatment in pain clinic, youth were randomized to one of two Internet treatments, WebMAP (adolescent and parent CBT pain intervention, n=138) vs WebED (education control, n=135). Close tracking and monitoring procedures led to an excellent retention rate in the trial (94.2% post-treatment, 92.4% at 6-months, and 92.4% at 12-months), and superb compliance (> 80%) with both treatment conditions (education
and CBT). In support of our primary hypotheses, youth receiving Internet CBT achieved greater improvement in pain-related disability compared to the Internet Education group from baseline to 6-month follow-up (b= -1.13, p = 0.03, d = -0.25). There were small effects of Internet CBT on improving depression in the Internet CBT group (relative to Internet Education) from baseline to post-treatment (b = -0.59, p = 0.04, d = -0.09). Similarly, adolescents receiving Internet CBT showed a significant reduction in pain-related anxiety relative to the Internet Education group from baseline to post-treatment (b = -1.33, p = 0.04, d = -0.13). As hypothesized, there were significant, small to medium effects of treatment on reducing maladaptive parent behaviors. Parents in the Internet CBT group demonstrated a significantly greater reduction in protective behaviors compared to the Internet Education group from baseline to post-treatment (b = -0.26,
$p < 0.001$, d = -0.49) and from baseline to six-month follow-up (b = -0.19, p = 0.001, d = -0.40). Effects were maintained through the 12-month follow-up 26. WebMAP has been adapted and tested in several other pediatric painful disorders including a completed trial in chronic headache 25, sickle cell disease (Palermo, et al, in press) and an ongoing trial with 300 youth with functional abdominal pain (NIH R01HD076983, PI: Lynn S. Walker). Our data and experience so far confirm WebMAP as an efficient, easily accessible tool with great potential to reduce pain-related disability and parental maladaptive behaviors that perpetuate and sustain painful disorders.

Pilot WebMAP study in children with ARP and CP. For this application, we collected preliminary data from WebMAP delivered to 2 youth with ARP and 4 youth with CP to assess feasibility and interest in learning cognitive-behavioral pain management skills. Youth were ages 11-16 years and recruited from Seattle Children's Hospital and University of Pittsburgh (2 of the 21 sites proposed in this application). Treatment engagement was good; youth logged into WebMAP an average of 8 times (range 2 - 21) and parents logged in an average of 10 times (range = 2 - 18) over the 8-10 week treatment period. Youth and parents completed a mean of 5.2 treatment modules (4 of 6 families completed the full program). On the Treatment Evaluation

Inventory, children's ratings indicated moderate acceptability (M = 28.2, scores > 27 indicate moderate acceptability). Similarly, parents rated moderate acceptability (M = 31.3). To understand participants' experience with WebMAP, we conducted qualitative interviews with 3 parent-child dyads. Overall, participants reported that the CBT program was a helpful tool for coping with pain. We learned that some children with ARP and their parents were less likely to complete the WebMAP program due to lack of experienced pain during the course of the intervention, which reduced the relevance of the treatment program. Because WebMAP is designed for treatment of chronic pain, this pilot work informed our decision to focus the proposed trial on youth with CP/ARP with pain frequency once per month or greater. Our preliminary data support that web-based self-management of pain is acceptable to children with CP/ARP and their parents.

2.3. Scientific or scholarly background:

Chronic pancreatitis causes significant burden in the pediatric population. Recent studies estimate an increase in the incidence of childhood acute pancreatitis (AP) at 3.6-16.1 cases per 100,000 children per year1, 2, which is similar to the incidences reported in adults 3. Most children with pancreatitis have a single acute episode that resolves without complications. However, 15-35% of children with AP develop acute recurrent pancreatitis (ARP) and some progress to chronic pancreatitis (CP, incidence ~0.5-2.73 per 100,000 per year) 4-7. Many children with CP/ARP are admitted to the hospital for recurrent attacks of AP 7. In the INSPPIRE cohort, children with CP/ARP have high disease burden, including abdominal pain, frequent emergency room visits, missed school days and recurrent hospitalizations 8, 9. The estimated average annual cost of pediatric CP/ARP is $40,589 per child in the INSPPIRE cohort 10. By extrapolating these costs, pediatric CP/ARP may result in ~ $64 million to the US healthcare system per year. Although relatively uncommon, pediatric CP/ARP is associated with high disease burden and healthcare costs.

The etiology of CP is complex. CP is a syndrome of progressive inflammation, remodeling, fibrosis and failure of the exocrine and endocrine pancreas over time. There are multiple etiologies linked to environmental and genetic factors, with genetics being a major factor in at least 75% of children 8, 9. Genetic factors define multiple pathogenic pathways, as well as disease modifiers and risk of complications, including fibrosis, diabetes, exocrine pancreatic insufficiency and pain 11. Thus, assessing genetic and environmental risk and mechanisms as cofactors in complex disease models is critical.

Pain is associated with high disease burden and economic costs in pediatric CP/ARP. Eighty-one percent of children report abdominal pain (~43% some form of constant pain) and pain is the major driver of cost in the INSPPIRE population 10. Children with constant pain experience more emergency room visits, miss more school, and require more hospitalizations compared to those without chronic pain 8, 10. Forty-one percent of children with CP in our cohort use an opioid to control pain. Despite the frequency of pain and its relevance to high socioeconomic burden, there are no non-pharmacologic pain interventions available for children with CP/ARP. As the disease progresses and pancreatic tissue is replaced with fibrosis, intrapancreatic nerves undergo neuropathic changes and become "sensitized" to transmit stimuli even after the painful stimulus is removed 12. This "central sensitization" is the main reason why pain persists even after the pancreas is resected 13, 14, rendering therapies such as total pancreatectomy and islet autotransplantation (TPIAT) ineffective for pain control for many patients. Children with chronic pancreatitis urgently need effective, early therapies delivered in childhood to reduce pain, pain-related disability and exposure to narcotics. Large and well-established cohorts, such as INSPPIRE allow us to test the effectiveness of non-pharmacological pain interventions in children with CP/ARP.

Impact of proposed project on improving scientific knowledge and clinical care. To maximize efficiency, this chronic pain self-management program is geared to the unique developmental and informational needs of youth with CP/ARP. The intervention is expected to enhance awareness and empower self-management early in the disease course. Given that the burden of pain worsens with age,

early intervention is critically important for interrupting negative cycles of pain and associated functional impairments. This will be the first project to
test the efficacy of an early, non-pharmacological pain intervention in children with CP/ARP and potentially to identify modifiers of treatment effects.

2.4. Prior approvals:
We conducted a pilot study IRB # STUDY00000137.

3. Study Endpoints[2]

3.1. Primary and secondary endpoints:

3.2. Primary or secondary safety endpoints:
For section 3.1: Primary endpoint is greater reductions in pain-related disability. Secondary endpoint is the reduction of pain, anxiety/depressive symptoms, opioid use, and HRQOL.
For section 3.2: There are no safety endpoints in this study.

4. Drugs, Devices and Biologics[3]

4.1. Manufacturer and name of all drugs, devices and biologics:
N/A

4.2. Description and purpose of all drugs, devices and biologics:
N/A

4.3. Regulatory status of all drugs, devices and biologics:[4]
N/A

4.3.1. Drugs or Biologics:
☐ IND Exempt. Explain:[5] ✍Click here to enter text.
☐ IND.

4.3.2. Devices:
☐ IDE Exempt. Explain:[6] ✍Click here to enter text.
☐ Abbreviated IDE / Non-Significant Risk. Explain:[7] ✍Click here to enter text.
☐ IDE / Significant Risk.

4.4. Plans to store, handle, and administer any study drugs, devices and biologics so they will be used only on subjects and be used only by authorized investigators:
N/A

5. Procedures Involved

5.1. Study design:[8]
A randomized controlled double-blinded trial will be conducted. Families will be randomized to either WebMAP or WebED (education control). 260 children (ages 10-19 years) with CP/ARP and their parents/caregivers (if possible) will be recruited from the INSPPIRE network and pancreatitis-related community organizations such as the National Pancreas Foundation (NPF) and Mission Cure. The intervention phase will last 8-12 weeks. Assessments will occur at baseline (T1), immediately after intervention (2 months; T2), and repeated at 6 months postintervention (T3) to assess maintenance of treatment gains. Primary outcome is pain-related disability (T2, T3).

5.2. Research procedures:[9]

Recruitment Study Procedure. 1) referral to the Web-MAP CP study by a collaborating INSPPIRE center or completion of community interest form, 2) telephone intake interview to determine study eligibility and explain study procedures, 3) coordinator will conduct informed consent over the phone and via secure REDCap link,

Study Procedure. 1) complete T1 (Baseline) study assessment via REDCap, 2) randomization to WebMAP or WebED program 3) phone instructional session for logging into the website and using the program. 4) participation in the randomized condition (see information below on each program), 5) complete T2 (about 2 months after baseline) via REDCap and 6) completing T3 6-month follow-up evaluation via REDCap.

Randomization Procedures. Using block randomization, children and parents will be randomized to two groups: WebMAP or WedED. Both groups will continue to receive standard medical care from a specialized pediatric pain clinic. We will generate a random numbers table using an online calculator to derive a randomization assignment in blocks of 4 for ID numbers.

WebMAP Group: The Web-MAP program teaches relaxation skills, pain coping strategies and parent behavioral and communication techniques to youth with chronic pain. Child participants will practice 8 skills. The skills included in Web-MAP are: 1) education about chronic pain and pain management, 2) recognizing stress and negative emotions, 3) relaxation and deep breathing, 4) implement coping skills at school, 5) cognitive skills, 6) lifestyle interventions, 7) staying active, and 8) relapse prevention. Parents will practice skills including: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) operant strategies I – attention and praise for positive coping, 4) operant strategies II –rewards for positive coping and reaching school goals, 5) modeling, 6) lifestyle, 7) communication, and 8) relapse prevention. Participants can also track daily activities and skills they used on the computer. Participants randomized to the WebMAP program will be practicing one of the 8 skills each week and will be contacted if they have not completed that skill after a week has passed. Mixed methods (email/text/phone calls if given permission by participant) will be used to contact participants to give reminders to continue logging into the program. Participants will receive their usual care and Web-MAP will not take the place of any aspect of their standard treatment

WebED Group. The purpose of the patient education control group is to control for time, attention, and computer usage. This group will serve as an attention control condition. Children will continue with the standard medical care that has been prescribed for their pain problem. Children and parents will be provided with access to a revised version of the Web-MAP study website, which will have two functional components: 1) information from publicly available educational websites about pediatric chronic pain management, 2) diary and assessments. This version of the website differs from the one accessed by the treatment condition in that it does not provide access to behavioral and cognitive skills training via treatment modules for children and parents.

During participation, a member of the study team would call/email/text to check in and to see if there are any problems or questions about using the program.

5.3. Data sources that will be used to collect data about subjects:[10]

Measures	Description	T1	T2	T3	Rater
Family Information Form	Parents report on demographic and socioeconomic information, and adolescent health history.	X			Parent
Pediatric Pancreatitis Questionnaire	Parents report on acute/chronic pancreatitis clinical history and diagnosis.	X			Parent
Pain Intensity, frequency, and duration	Pain intensity will be rated on the online diary using an 11-point NRS. Pain frequency and duration are averaged over each seven-day measurement period.	X	X	X	Child
Child Activity Limitation Interview (CALI-9)	Daily diary version of the CALI-9 will be used to rate perceived difficulty in completing 9 daily activities as a measure of pain-related disability.	X	X	X	Child
PROMIS Pediatric Emotional Distress Scales	8-item scale of anxiety that assesses fear (e.g., fearfulness), anxious misery (e.g., worry) and hyperarousal (e.g., nervousness) and 8-item scale of depressive symptoms.	X	X	X	Child
Pain Self-Efficacy	The Pain Self-Efficacy Scale is a 7-item measure that assesses the child's beliefs in carrying out activities when in pain. The scale has demonstrated good internal consistency, cross-informant reliability with parent report, and strong construct validity.	X	X	X	Child
PROMIS Pain interference	Pediatric Short Form assesses pain-related interference	X	X	X	Child
Bath Adolescent Pain Questionnaire–Parent Impact	Assesses changes in perception of burden, family functioning, and emotional distress associated with parenting youth with chronic pain.	X	X	X	Parent
Health-related quality of life	Pediatric Quality of Life Inventory will assess broad impact of health on child and family	X	X	X	Parent, Child
Health services utilization	Client Services Receipt Inventory for Pain assesses inpatient and outpatient visits, medications, other treatments, and indirect costs as reported by the parent	X		X	Parent
Treatment satisfaction and engagement	Treatment satisfaction (10 item measure with Likert ratings and open-ended items about content and delivery method) (P, A); Web usage		X		n/a

	(logins, completion of assignments, etc.) collected from the administrative website				
Adverse events	Adverse event form will be used.		X	X	Parent, Child
Abdominal Pain Index	Assesses child abdominal pain frequency, duration, and intensity.	X	X	X	Parent, Child

Information collected from INSPPIRE 2 study will be used in this study. This information includes information about abdominal pain, frequency and severity of pancreatitis attacks, treatments used, hospital and emergency room visits, and blood draw for testing subjects' CP genetic variants. This information will not be collected for community participants who are not involved in INSPPIRE2.

5.4. Data to be collected, including long–term follow–up data:[11]

Data will be collected at three time points. Assessments will occur at baseline (T1), immediately after intervention (about 2 months; T2), and repeated at 6 months postintervention (T3).

6. Data and Specimen Banking[12]

6.1. Complete list of the data and/or specimens to be included in the bank:[13]

N/A

6.2. Location of data and/or specimen storage:[14]

N/A

6.3. List of those with direct access to data and/or specimens in the bank:

N/A

6.4. Length of time data and/or specimens will be stored in the bank:

N/A

6.5. Procedures for protecting the confidentiality and privacy of the subjects from whom the data and/or specimens were collected:[15]

N/A

6.6. How the data and/or specimens will be made available for future use:

N/A

6.6.1. Who can request data and/or specimens from the bank:

N/A

6.6.2. Format in which data and/or specimens will be provided:

N/A

6.6.3. Process for investigators to request data and/or specimens:[16]

N/A

6.6.4. Restrictions on future use:[17]
N/A

6.6.5. Plan for providing data results from banked data/specimens:
N/A

7. Sharing of Results

7.1. Plan to share results with subjects/others:[18]
Study results will be shared with all enrolled participants after active participant study involvement is complete and study analyses are finished. These results would be in the form of a one-time letter outlining study findings (sent via email).

8. Study Timelines

8.1. Duration of an individual subject's participation in the study:
Approximately 9 Months

8.2. Duration anticipated to enroll all study subjects:
Approximately 3 years

8.3. Estimated date for the investigators to complete this study:
This will be a 5 year study so approximately Winter 2024

9. Study Population[19]

9.1. Inclusion criteria for each subject population (e.g., patients, parents, providers):
Study participants in the RCT will include 260 children with chronic or acute recurring pancreatitis, along with one participating parent/caregiver. Youth age 18 or 19 can enroll in the study even if they do not have a parent/primary caregiver who can participate. Inclusion criteria include: (a) diagnosis of CP or ARP, (b) ages 10-19 years, (c) at least 4 AP flare-ups/attacks in past year, or at least 1 instance of moderate (4/10 pain) pancreatitis/abdominal pain in the past month, and (d) access to the Internet on any web-enabled device.

9.2. Exclusion criteria for each subject population:
Exclusion criteria include parent report of the following: (a) non-English speaking, (b) inability to read at the 5th grade level due to learning or developmental delays; (c) children with cystic fibrosis who have pancreatic insufficiency at the time of diagnosis; (d) patients with Shwachman-Bodian-Diamond Syndrome; (e) ARP with no evidence of chronic or persistent pain. (f) anticipated surgery (TPIAT or other) during study participation (6 month timeframe); (g) other severe systemic disease.

9.3. Vulnerable populations involved in the study:[20]
☒ Children/Teenagers[21]
Risk assessment specific to this vulnerable population and additional safeguards:[22]
The research is considered minimal risk as the probability and magnitude of psychological and physical risks anticipated in this research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The relaxation skills and pain coping strategies taught in the online program is comparable to what is taught within clinical programs. The participant has the option of withdrawing participation at any time during the study. Knowledge gained through this research will guide future research and interventions to help adolescents with chronic pancreatitis.

☐ Children who are Wards of the State[23]
Risk assessment specific to this vulnerable population and additional safeguards:
N/A

☐ Adults Unable to Consent[24]
Risk assessment specific to this vulnerable population and additional safeguards:
N/A

☐ Neonates of Uncertain Viability or Non–Viable Neonates[25]
Risk assessment specific to this vulnerable population and additional safeguards:
N/A

☐ Pregnant Women[26]
Additional safeguards:
N/A

☐ Prisoners[27]
Additional safeguards:
N/A

10. Number of Subjects

10.1. Total number of subjects to be enrolled locally:[28]
30 dyads- children with CP/ARP and their parents/caregivers (if available)

10.2. Total number of subjects to be enrolled across all participating sites:[29]
260 dyads- children with CP/ARP and their parents/caregivers (if available)

10.3. Number of screened subjects versus the actual number enrolled in the research:[30]
We anticipate that screening 381 children with CP/ARP will enable us to enroll 260 into this study.

10.4. Power analysis:
Based on our historical data, the estimate of the standard deviation for the primary outcome pain-related disability is approximately 4. We expect a difference of 1.5 between WebMAP and WebED in the mean score of pain-related disability. At the significance level of 0.05, we need 112 subjects per group to have 80% power to detect a difference. Results indicate sufficient power to detect relatively small differences between children receiving WebMAP compared to WebED. Taking into account 10-15% attrition, we will enroll 130 patients per group. Because Aims 2 and 3 employ the LMM regression approach, the power calculation is complicated and requires re-specifying model parameters that are virtually unknown a priori. Therefore, we take a simple approach based on correlation coefficient. Given the sample size of 112 subjects, we have 80% power to detect the correlation of 0.27 between gene (or baseline clinical characteristics) and pain-related disability, at the significance level of 0.05. As the LMM is more efficient, the actual power will be greater. Power to detect correlations between genetic/clinical characteristics and pain-related disability may be lowered depending on the number of community participants enrolled.

11. Withdrawal of Subjects

11.1. Anticipated circumstances under which subjects will be withdrawn from the research without their consent:

The PI may decide to withdraw participants from the study if a family is not able to comply with study procedures or do not understand study instructions.

11.2. Procedures for orderly termination:

If a participant must be withdrawn from all study procedures the study staff would contact the family to explain the cause for study withdrawal and finalized study termination.

11.3. Procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and withdrawal from data/specimen banking:

Full Withdrawal: If a participant must be withdrawn from all study procedures the study staff would contact the family to explain the cause for study withdrawal and finalized study termination.

Partial Withdrawal: If a participant partially withdraws from the procedures, study staff would contact the family to discuss family's interest in participation. If the family is interested, the study procedures will be continued, if the family is not interested, this will be considered a full withdrawal.

12. Risks to Subjects

12.1. Reasonably foreseeable risks to subjects (include each study population, each arm, and optional procedures):

This study is minimal risk. There are potential risks around emotional distress, time commitment, and confidentiality. Although asking about physical symptoms and mood/behavior does not typically result in any distress, there is a small risk of emotional distress. There is a potential risk of loss of confidentiality.

12.2. Procedures with unforeseeable risks:

N/A

12.3. Procedures with risks to an embryo or fetus should the subject be or become pregnant:

N/A

12.4. Risks to others who are not subjects:

N/A

12.5. Procedures performed to lessen the probability or magnitude of risks:

Participants will be advised they can skip any questions they feel uncomfortable answering. To support confidentiality, adolescents will be asked to complete questionnaires independently. We will make every effort to protect this data. For example, all data will be coded with a unique ID number. Participants will be informed of their right to refuse to participate in any part of the data collection and given the phone numbers of the PI and the Seattle Children's IRB in the event that they desire further information or would like to issue a formal complaint.

13. Potential Benefits to Subjects

13.1. Potential benefits that individual subjects may experience from taking part in the research:[31]

Participation in this research study may or may not benefit the subject. The 8-week Web-MAP program may help to increase daily functioning and decrease pain intensity in children and teens who complete this program as it has shown effectiveness in other youth with chronic pain.

14. Data Analysis/Management

14.1. Data analysis plan, including statistical procedures:

Distributions of primary and secondary outcome variables at each time point (and on difference scores between time points) will be examined first with summary statistics and graphical tools. For outcome variables with highly skewed distributions, we will either apply transformation or non-parametric test procedures. Preliminary work will also involve computation of scale reliabilities (e.g., internal consistency using Cronbach's alpha) of all of the self report measures. The RCT analysis will be an intent-to-treat analysis including all randomized subjects. Two-sample t-test will be used to test the difference between the WebMAP group and WebED group in pain-related disability and other outcomes (e.g., anxiety, depression and HRQOL) at baseline, 2 months and 6 months. In the case that the outcome is categorical, the chi-squared test will be used. The pre-post change in pain-related disability will also be assessed within and between groups using one-sample or two-sample t-test. Linear mixed models (LMM) will be further used to compare the change in pain-related disability over time (from baseline to follow-ups) between WebMAP and WebED. The LMM is ideally suited for analysis of repeated measures because it allows for more specific estimation of the correlation structure of the residuals, it efficiently handles unbalanced designs and missing data, without excluding participants or imputing values. The repeated measures of pain-related disability will be treated as the dependent variable. Measurement time, intervention condition, and their interaction will be included in the LMM as covariates. We will include biological covariates of age and sex in all models and will include other demographic and clinical factors, as needed to adjust for potential confounding effects. Fit statistics (e.g., Akaike's Information Criterion) will be evaluated for all models to ascertain the best fit of the correlation structure of the dataset. We will use a computer program, PROC MIXED (SAS v9.3 SAS Institute Inc, Cary, NC) to estimate and test the models with continuous dependent measures. Results will be summarized with the estimates of model parameters and p-values. For a binary endpoint of clinically significant reduction in pain (i.e., achieved 50% or greater reduction in pain intensity), we will employ the generalized linear mixed model (GLMM) to model and compare the changes over time (from baseline to follow-ups) between WebMAP and WebEd. We will use SAS PROC GLMIMX, which provides an adaptation to the LMM approach for categorical data.

Blood draw and collection will be done by the INSPPIRE 2 study, but will not be done for patients recruited from community organizations who are not participating in INSPPIRE 2. The data we need will be pulled from that study for analysis. LMM will be our primary analytic tool to investigate the association between genetic co-variants and treatment response in internet-based CBT. In the LMM, repeated measures of painrelated disability will be used as the dependent variable. The covariates include time, gene and demographic variables (e.g., sex) when necessary. In the initial evaluation, "genetic signatures" will be used as covariants. This approach markedly reduces complexity by combining known pathogenic variants in a class into an object such as "CFTR-related disorders", "Pathologic Trypsins", "Unfolded protein response (UPR)", "Lipotoxicity", "idiopathic" and "others" for etiology, as well as "opiate pharmacogenetics defect", "pain receptor" and others for modifiers. In addition, pathogenic variants with large effects (e.g. PRSS1 p.R122H, SPINK1 p.N34S) or high frequency (e.g. CTRC g.60G haplotype) will be evaluated as independent covariates. To investigate multiple genes and genetic signatures, we will conduct univariate gene analysis by regressing each gene independently on the pain-related disability outcome to see if there is reasonable signal of association between the gene and pain-related disability. Using this procedure, we screen out the genes with p value > 0.1. We then build

a multivariate model based on the genes with p value < 0.1 in the univariate analysis. In the case that the number of genes included in the multivariate model is still large, model selection (e.g., using LASSO) will be performed to obtain a parsimonious model and identify the genes that are significantly associated with the outcome pain-related disability. Further analysis utilizing machine learning programs for cluster analysis, such as principle component analysis, will be conducted as complementary and confirmatory analyses.

14.2. Quality control procedures for collected data:[32]

The PI will supervise the study coordinator in collating and storing data and overseeing the integrity of study records. Data will be maintained on a network server with password protection and daily backup of data performed. The primary source of data will come from online assessments conducted on the REDCap website provided through ITHS at UW. REDCap has extensive security precautions appropriate for the storage of PHI. REDCap was developed specifically around HIPAA-Security guidelines and is recommended for use by researchers. In 2010 the Institute of Translational Health Sciences Biomedical Informatics Core (ITHS BMI) began supporting an installation of REDCap (Research Electronic Data Capture), which is software specifically designed for electronic data capture (EDC) for clinical trials. REDCap features include differentiated user roles and privileges, user authentication and authorization security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes. PIs can configure REDCap User Rights and Data Access Groups to provide granular study data access to authorized study personnel. Access to servers is restricted to authorized ITHS BMI support personnel. The servers are located on ITHS-owned hardware in a secure server room at the University of Washington. This server room meets the technical requirements for HIPAA compliance and hosts other servers containing Protected Health Information (PHI). The Operating System of each server will be kept fully patched and firewalled in accordance with UW Medicine Information Security Policy. All identifying information will be removed from all electronic data, thus protecting the identities of participating families. Data will be kept for a minimum of seven years.

To ensure the accuracy of the data the following processes will be implemented:

- The study coordinator will check all data from REDCap questionnaires for completeness.
- REDCap will be exported directly to SPSS statistical software, to ensure the participant's responses are accurately entered into the database used for analyses. This will be secure and stored locally at Seattle Children's.

15. Confidentiality[33]

15.1. Procedures to secure the data and/or specimens during storage, use, and transmission:

All participant data will be coded with a unique identification number, thus ensuring the subject's identity as a participant in this study will remain confidential. The research records will be kept confidential and protected health information will be safeguarded as required by Seattle Children's IRB and HIPAA regulations. The research staff and Seattle Children's IRB will be allowed to inspect the information collected from this study. Data collection online through REDCap will also be private and confidential. REDCap was developed specifically around HIPAA-Security guidelines and is recommended for use by researchers. In 2010 the Institute of Translational Health Sciences Biomedical Informatics Core (ITHS BMI) began supporting an installation of REDCap (Research Electronic Data

Capture), which is software specifically designed for electronic data capture (EDC) for clinical trials. REDCap features include differentiated user roles and privileges, user authentication and authorization security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes. PIs can configure REDCap User Rights and Data Access Groups to provide granular study data access to authorized study personnel. Access to servers is restricted to authorized ITHS BMI support personnel. The servers are located on ITHS-owned hardware in a secure server room at the University of Washington. This server room meets the technical requirements for HIPAA compliance and hosts other servers containing Protected Health Information (PHI). The Operating System of each server will be kept fully patched and firewalled in accordance with UW Medicine Information Security Policy.

15.2. Location where the data and/or specimens will be stored:

All contact information and identifying data will be stored in a secure location within the PI's research lab

15.3. Length of time data and/or specimens will be stored:

Data will be kept for a minimum of seven years.

15.4. Individuals with access to data and/or specimens:

Only the research staff and Seattle Children's IRB will be allowed to inspect the information collected from this study

15.5. Process for the transmission of data and/or specimens outside Seattle Children's:

15.5.1. List of data and/or specimens that will be transmitted:

N/A

15.5.2. Individual(s) who will transmit data:

N/A

16. Provisions to Monitor Data to Ensure the Safety of Subjects[34]

16.1. Plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe:[35]

N/A

16.2. Data reviewed to ensure safety of subjects:

N/A

16.3. Safety information collection procedures:

N/A

16.4. Frequency of cumulative data review:

N/A

16.5. Conditions that trigger an immediate suspension of the research:

N/A

17. Use of Social Media

17.1. Types of social media to be used and how:
Facebook, Instagram, Twitter, and LinkedIn will be used for recruitment purposes only - to share the study flyer information and provide a link to a REDCap community interest form where potential study participants can contact the study team if interested.

17.2. Measures in place to protect the privacy or confidentiality of subjects:[36]
The only transmission of confidential information will occur via secure REDCap form. This will only happen when a community member is interested in the study and voluntarily discloses this information to the study team with the intention of being contacted about the study.

17.3. Types of communications that will be submitted to the IRB for review:[37]
All study information included on social media websites will be copied from the IRB reviewed/approved study flyer. Advertisements for Facebook, Twitter and Instagram will be submitted to the IRB for their review.

17.4. If user-generated content will be active, how it will be monitored and what actions will be taken to ensure subject safety and study integrity:
N/A

18. Research Related Injury[38]

18.1. Available compensation in the event of research related injury:
N/A

19. Recruitment Methods[39]

19.1. When, where, and how potential subjects will be recruited:
Child participants with CP/ARP will be recruited from one of the 21 sites in the INSPPIRE cohort registry. Potential participants who are participating in the INSPPIRE 2 study and have consented to the sharing of their contact information for related research studies will be referred by their provider/research coordinator at their institution. Referring staff will send the potential participating family's contact information to the study team at Seattle Children's via secure email or REDCap form. The potential participant will be sent a letter and flyer describing the study, then if unresponsive, will be contacted over the phone/email/text by Seattle Children's to screen for eligibility and assess interest. We will contact participants up to 8 times in total, spread out over a period of 8 weeks. Participants will be given multiple opportunities to opt out of future contact, in their introductory letter and future contact attempts. Based on our prior experience recruiting from this population, this number of contact attempts is often necessary to make contact, even if patients have been referred by their provider after explicitly expressing interest. Fewer attempts would significantly reduce our chances of reaching a family. Furthermore, this study has potential to directly benefit patients. If participants are interested and eligible, consent forms will be emailed to participants and a consent call will be set up for a future time.

INSPPIRE2 participants who enroll in this study will be contacted to see if they would like to participate in a brief related follow-up study, STUDY00002765. This study consists of a single survey. See the STUDY00002765 protocol and related documents for further details about how these participants will be contacted. STUDY00002765 is conducted by the same PI and study team members.

Additional community participants will be identified via the websites and social media outlets (Facebook, Instagram, and Twitter) of pancreatitis patient advocacy groups such as the National Pancreas Foundation (NPF) and Mission Cure, through advertisements on Facebook

and Instagram, and through distribution of study flyers via interested gastroenterology clinics/providers. These participants will be able to view the study flyer, and if they are interested in participating, they may "self-refer" by filling out a secure REDCap form with their contact information and a few preliminary eligibility questions (see separate form). They may also call SCH staff directly if they have questions about the study. SCH staff will then contact these potential participants and screen them for eligibility over the phone/email/text. If eligible, consent forms will be emailed to participants and a consent call will be set up for a future time.

Additional potentially eligible participants will be identified from SCH clinic schedules and electronic medical records. Potential participants and their parents will receive an initial mailing with a letter informing them of potential study eligibility and giving them the option to decline contact. This letter will also include a flyer outlining study details. All potential participants will be approached two weeks after mailing the letter with a phone call, email, or text message from study staff inviting them to participate, screening for eligibility criteria, and completing the consent process for participants who agree to participate. Study staff will attempt to contact potential participants a total of three times over the phone, email, and/or text message.

19.2. Steps that will be taken to protect potential subjects' privacy interests:[40]

All information will be stored and transmitted securely through REDCap. Participants will be given opportunities to decline any further contact.

Recruitment of patients will involve private mailings to their home and private phone calls, emails or text messages. Families have the option of calling to decline participation and any further contact before they are contacted via phone. Consent will take place in the privacy of the participants' home after the family has had sufficient time to decide whether or not they would like to participate. There is no time constraint on a parent or youth's decision to participate, families can take as much time as they need to review consent/assent documents and ask questions about the study. In addition, study staff will emphasize participation in this study is voluntary and will not impact the patient's care.

19.3. Sources of subjects:[41]

Child participants will be receiving care from one of the 21 sites in the INSPPIRE cohort registry. Additional participants will be recruited from patient advocacy groups such as the NPF or Mission Cure, social media advertisements, and through gastroenterology clinics. Additional participants will be identified through SCH clinic schedules and records.

19.4. Methods that will be used to identify potential subjects:

Potential subjects will be identified if they are already part of the INSPPIRE2 study and receiving care, if they respond to online advertisements through patient advocacy groups/social media, or if they respond to flyers at their gastroenterology clinic, or if they have sought care for acute recurring/chronic pancreatitis at SCH (through SC clinic schedule and medical records

19.5. Materials that will be used to recruit subjects:[42]

INSPPIRE2 participants will receive a study flyer and letter describing the study.

Some participants will receive a flyer from a patient advocacy group website/social media site/GI clinic, and will fill out a secure REDCap community interest form to pass their contact information on to Seattle Children's staff it they are interested in participating.

SCH patients will receive a letter from the study team and a study flyer for their initial contact.

The study team will use phone calls/voicemails (recruitment script), and/or email/text messages to approach subjects who are referred, self-referred, or identified from SC clinic schedules/medical records.

19.6. Recruitment methods not controlled by Seattle Children's:
N/A

20. Consent/Assent Process

20.1. Where the consent process will take place:
Consent will take place over the phone, after the family has had sufficient time to decide whether they would like to participate.

20.2. Steps that will be taken to protect prospective subjects' privacy interests:[43]
Consent will be done over the phone while the participant is in the privacy of their own home.

20.3. Waiting period available between approaching a prospective subject and obtaining consent:
Each participant will be given sufficient time to read, review and ask questions before obtaining consent.

20.4. Process to ensure ongoing consent:

We will ask youth and parents questions about the study so they fully understand their involvement over the course of the study. We will be touching base with them at each time point to answer questions and let them know next steps.

20.5. If this box is checked, "SOP: Informed Consent Process for Research (HRP-090)" will be followed: ☒

20.6. If "SOP: Informed Consent Process for Research (HRP-090)" will not be followed, address the following:[44]

20.6.1. Role of the individuals listed in the application as being involved in the consent process:
N/A

20.6.2. Time that will be devoted to the consent discussion:
N/A

20.6.3. Steps that will be taken to minimize the possibility of coercion or undue influence:
N/A

20.6.4. Steps that will be taken to ensure the subject's understanding:
N/A

20.7. Non-English Speaking Subjects[45]

20.7.1. Language(s) other than English are understood by prospective subjects or representatives:

N/A

20.7.2. If non-English speaking subjects will be included in the research (check one):

☐ Appendix A-10 of the Investigator Manual will be followed[46]

☐ Appendix A-10 of the Investigator Manual will not be followed. Explanation of procedures not following Appendix A-10:
✍Click here to enter text.

20.7.3. Justification if non-English speaking subjects will be excluded from the research:[47]
The WebMAP program is only available in English.

20.8. Subjects Who Are Not Yet Adults (Infants, Children, Teenagers)

20.8.1. Process used to determine whether an individual has not attained the legal age of consent under the applicable law of the jurisdiction in which the research will be conducted (e.g., individuals under the age of 18 years):[48]
We will be collecting date of birth to determine age. Parent consent for their participation will be obtained for all individuals under the age of 18.

20.8.2. Parental permission will be obtained from:[49]

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☒ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Neither parent.[50]

20.8.3. Process used to determine an individual's authority to consent to each child's general medical care if permission will be obtained from someone other than parents:[51]
Caregivers who are not biological parents must be legal guardians in order to participate in the study and provide consent for their child's participation.

20.8.4. Assent will be obtained from:[52]

☒ All children.

☐ Some children. Specify: ✍Click here to enter text.

☐ None of the children. Explain: ✍Click here to enter text.

20.8.5. Procedures for obtaining and documenting assent:
Consent forms will be read and completed at the participants' home, while speaking to a SCRI study coordinator on the phone. This phone conference will be used to answer additional questions, further explain the study, and obtain consent. After going through the consent script, participants will be asked to indicate their consent and authorization on an electronic form.

During the consent script, the study coordinator will discuss information about study procedures, study risks, potential benefits, and the voluntary nature of the study. In

addition, the study coordinator will assess how well potential participants understand the study through the types of questions raised during the discussion of the protocol. The study coordinator will use lay language when speaking with the participant (and parent). For participants under 18, the study coordinator will obtain consent of the parent first. The study coordinator will document the day and time of consent in the participant database. The participant will then be asked to document their consent on a secure electronic form via REDCap. The process will take about 20-30 minutes.

If a phone conference cannot be arranged at the same time for the parent and child participants, the study coordinator will speak with the parent and child separately over the phone. The study coordinator will only speak with the child after speaking with the parent.

20.8.6. Plan for re-approaching children who have reached the age of majority to obtain consent:[53]

It is possible that some child participants will turn 18 between the time they are enrolled in the study and the time they complete follow-up assessments. If this occurs, these participants will be re-approached when they are scheduled to complete a follow-up. If they are still interested in participating in the study, we will send these participants a study consent form and obtain their electronic signed re-consent to continue participating in the study, if they are still willing.

We will obtain a waiver of re-consent for participants who reach the age of majority after their study participation is complete and prior to completion of the study and data analysis.

20.9. Cognitively Impaired Adults/Adults Unable to Consent[54]

20.9.1. Process used to determine whether an individual is capable of consent:

Cognitively impaired adults/adults unable to consent will not be enrolled in the study.

20.9.2. Individuals from whom permission will be obtained in order of priority:[55]

N/A

20.9.3. Assent will be obtained from:

☐ All of these subjects.
☐ Some of these subjects. Specify: ✍Click here to enter text.
☐ None of these subjects. Explain: ✍Click here to enter text.

20.9.4. Process for obtaining and documenting assent:[56]

N/A

20.10. Waiver or Alteration of Consent Process

20.10.1. Reasons for requesting a waiver or alteration of informed consent:[57]

We are requesting a waiver of consent for children who turn 18 whose private identifiable information is still being used for data analysis purposes, but are no longer actively participating in the study. The justifications for this waiver are here:

20.10.2. Consent Waiver/Alteration Criteria justifications:[58]

20.10.2.1. The research involves no more than minimal risk to the subjects because:

Participants are only asked to complete online surveys and log in to a website that would provide either education about chronic pain or skills training to manage chronic pain. There are no significant risks involved in participation. Furthermore, data analysis involves no additional risk to participants whatsoever, as participants do not complete any activities and are no longer involved.

20.10.2.2. The waiver or alteration will not adversely affect the rights or welfare of the subjects because:[59]

The waiver of consent would not adversely affect the rights or welfare of subjects because any publication of research results would never reveal an individual's identity either directly or indirectly. Furthermore, all survey responses will be linked with a unique study ID to protect participant confidentiality, and all study documents/information will be stored in secure, password/firewall-protected servers and databases.

20.10.2.3. The research could not practicably be carried out without the waiver or alteration because:[60]

Due to the age range of the study, most participants would turn 18 before data collection & analysis is complete, so the research could not be practicably carried out if the study team had to contact all of them again and re-consent. Additionally, study staff will not be in contact with participants after their study participation is complete, and it would be impracticable to conduct the research if the study team had to reach participants for the purposes of obtaining consent due to significant time lapse between participant completion, turning 18, and data collection/analysis, along with changing contact information or life circumstances. In addition, not including data from the entire participant population would bias study results.

20.10.2.4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

N/A

20.10.3. If the research involves a waiver of the consent process for emergency research, provide sufficient information for the IRB to make it determinations:[61]

N/A

21. Process to Document Consent in Writing

21.1. If consent will be documented in writing (check one):

☐ "SOP: Written Documentation of Consent (HRP-091)" will be followed.

☒ "SOP: Written Documentation of Consent (HRP-091)" will not be followed.

Process of documenting consent:[62]

The study coordinator will document the day and time of consent in the participant database. The participant will then be asked to document their consent on an electronic form via REDCap,

21.2. If consent will not be documented in writing (check all boxes that apply):[63]

- ☒ A written statement/information sheet describing the research will be provided to subjects.[64]
- ☐ A written statement/information sheet describing the research will not be provided to subjects. Explain: ✍Click here to enter text.
- ☐ A consent script will be used.[65]

22. HIPAA Authorization and RCW Criteria

22.1. HIPAA Authorization (check all boxes that apply):

- ☐ The study does not involve the receipt, creation, use and/or disclosure of protected health information (PHI).[66]
- ☐ HIPAA authorization will be obtained as part of a signed consent form.
- ☒ The study will access PHI without prior authorization from subjects (including for recruitment purposes – e.g., reviewing the medical record to determine eligibility). *See 21.2 below for required HIPAA waiver/alteration criteria*.
- ☒ Subjects will review a written statement/information sheet with the appropriate HIPAA language but will not provide a written signature. See 21.2 below for required *HIPAA alteration criteria*.[67]
- ☐ Other. Explain:[68]
  ✍Click here to enter text.

22.2. HIPAA Waiver/Alteration Criteria: Explain why:

22.2.1. The use or disclosure of PHI involves no more than a minimal risk to privacy of individuals, based on, at least the presence of the following elements:

22.2.1.1. An adequate plan to protect the identifiers from improper use and disclosure:

We will protect all identifiers by using unique study ID numbers on all PHI and only study team members will have access to a subject's PHI and ID number.

22.2.1.2. An adequate plan to destroy identifiers at earliest opportunity consistent with conduct of research:

All identifiers will be destroyed at the earliest opportunity consistent with conduct of this research.

22.2.1.3. Assurances that PHI will not be reused or disclosed to any other party or entity, except as required by law or for authorized oversight of the research:

PHI will not be reused or disclosed to any other person or entity.

22.2.2. The research could not practicably be conducted without the waiver or alteration of authorization:

Without the alteration of authorization, study sites would not be able to obtain patient contact and eligibility information. The study would have limited eligible patients if patients were given the option to contact the study staff first. Study staff

would not be able to contact potentially eligible participants for screening purposes without access or use of their PHI. Obtaining PHI is necessary for the characterization of the groups of the individuals who screen out of the study. Since we will not be seeing the participants in person, we are asking for the waiver for online authorization. Without it, study time lines would be delayed and participant interest would decrease waiting for mailed consent forms. The participant will document their consent on a secure electronic form via REDCap that meets state/international laws.

22.2.3. The research could not practicably be conducted without access to and use of the PHI:[69]

The nature of this research is specific to the participant's health.

23. Payments/Costs to Subjects[70]

23.1. Amount, method, and timing of payments to subjects:[71]

Youth and parents will each receive a $50 electronic gift card for each timepoint assessment they complete. They will receive this gift card after completing each time point.

23.2. Reimbursement provided to subjects:[72]

N/A

23.3. Additional costs that subjects may be responsible for because of participation in the research:[73]

We do not anticipate any costs.

24. Setting

24.1. Site(s) or location(s) where the research team will conduct the research:

SCRI study staff will receive referrals from the participating clinics. All survey assessments/diaries will be sent via REDCap/WebMAP for participants to complete in their home.

24.2. Composition and involvement of any community advisory board:

N/A

24.3. For research conducted outside of the organization and its affiliates:[74]

24.3.1. Site-specific regulations or customs affecting the research:

N/A

24.3.2. Local scientific and ethical review structure:

N/A

25. Resources Available

25.1. Qualifications (e.g., training, education, experience, oversight) of investigator(s) to conduct and supervise the research:[75]

The PI and study staff of SCRI have years of experience in the recruitment methods used in this study and skills needed to organize, track, and follow this many participants through the completion of the study. All study procedures will be done under the supervision of the PI who assumes responsibility for all study related actions and events. The PI will be available to clarify recruitment eligibility, answer questions, etc. throughout the course of the study.

25.2. Other resources available to conduct the research:[76]

As this study presents minimal risk to participants, we do not anticipate participants needing medical or psychological resources consequently to study procedures. However, if a participant voluntarily requests additional services, the study team will provide SCH-based or community-based resources

26. Coordinating Center Procedures

26.1. Coordinating center institution:

Seattle Children's

26.2. If Seattle Children's is the coordinating center:

26.2.1. Process to ensure communication among sites:[77]

We will hold monthly between site investigator phone meetings. to discuss study progress, answer questions, and ensure proper study conduct.

26.2.2. Process to ensure all site investigators conduct the study according to the IRB approved protocol and report all non-compliance:

Our monthly calls will be to discuss study progress, answer questions, and ensure proper study conduct.

26.2.3. Process to ensure all required approvals are obtained at each site:

Before beginning the research, we will ensure that required approvals have been obtained at all sites, and we will maintain a record of their approvals including all modifications.

26.2.4. Process to ensure all sites are informed of any problems and/or interim results:

These will be discussed at monthly phone meetings.

27. Good Clinical Practice

27.1. If you have committed to conducting the described study per International Center for Harmonization of Good Clinical Practice (ICH-GCP), check this box: ☐[78]

[1] Include information if this protocol is associated with other IRB-approved studies (e.g. is this application the next part/phase of a previously approved application.
[2] In clinical trials, an endpoint is an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.
[3] Include information on a drug or biologic in this section if: (1) the study specifies the use of an approved drug or biologic; (2) the study uses an unapproved drug or biologic; (3) the study uses a food or dietary supplement to diagnose, cure, treat, or mitigate a disease or condition; or (4) data regarding subjects will be submitted to or held for inspection by the Food and Drug Administration (FDA). Only include information on a device in this section if: (1) the study evaluates the safety or effectiveness of a device; (2) the study uses a humanitarian use device (HUD) for research purposes; or (3) data regarding subjects will be submitted to or held for inspection by the FDA. Please note that mobile medical applications may meet the definition of a device – see FDA Guidance.
[4] See the Investigator Manual HRP-103 for sponsor requirements for FDA-regulated research.
[5] Explain what IND exemption category applies to the drug and why. Note that a drug is not exempt from an IND unless all criteria for one category are met. See "HRP-306: Drugs" for more information.
[6] Explain what IDE exemption category applies to the device and why. Note that a device is not exempt from an IDE unless all criteria for one category are met. See "HRP-307: Devices" for more information.
[7] Explain why the device is NOT a significant risk device. A significant risk device means an investigational device that: (a) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (b) is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (c) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (d) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
[8] Be sure to indicate if controls will be included and include information about why control arms are ethically acceptable.
[9] Describe all of the research procedures being performed. Be sure to make it clear which procedures apply to each subject population. When applicable, describe how research procedures differ from standard of care and/or affect standard of care. Describe any audio/video recording that will be involved.
[10] Attach all surveys, scripts, and data collection forms to the "Supporting Documents" page.
[11] Include information about the frequency of data collection.
[12] See HRP-001 - SOP – Definitions for definition of banking. Type N/A if not applicable. If the data is subject to NIH Genomic Data Sharing Policies (e.g. you will submit data to dbGaP, NDAR, FITBIR), indicate here.
[13] If applicable, include a list of identifiers that will be banked.
[14] Be general (e.g., researchers' lab, clinic, etc.)
[15] Generally, data and/or specimens should be released in a coded, non – identifiable manner.
[16] Include a description of the process used to verify and document that any required approvals have been obtained prior to release of data/specimens from the bank.
[17] You can allow for use for broad purposes
[18] This includes putting results and/or data in the subject medical records.
[19] If your population will differ from the representative population where the study will take place (e.g., race, ethnic group, or gender), provide a rationale for the differences.
[20] If you check a box below, be sure to include the additional safeguards associated with the population.
[21] Refer to HRP-416 CHECKLIST: Children.
[22] If the study is minimal risk, explain why. Must also include, as applicable: (1) why direct benefits are anticipated, (2) why risks are justified by anticipated benefit and/or the relationship between risk and prospective benefit compared to available alternatives, (3) why risk represents only minor increase over minimal risk, (4) how study procedures are reasonably commensurate with those inherent to the child's actual or expected conditions, (5) whether the interventions/procedures are likely to yield generalizable knowledge about the participant's condition and why it is of "vital importance" to understanding or amelioration of the participant's underlying disorder or condition, and (6) an explanation of what alternative methods/approaches were considered to make the above assessments (as applicable).
[23] This population may be wards of the state or any other agency, institution, or entity. Refer to HRP-416 CHECKLIST: Children, Section 6, for additional guidance on required considerations for this population.
[24] This refers to both cognitive impairments and adults who are incapacitated for any other reason. As applicable, refer to HRP-417 CHECKLIST: Cognitively Impaired Adults.
[25] Refer to HRP-413 CHECKLIST: Neonates and HRP-414 CHECKLIST: Neonates of Uncertain Viability.
[26] Refer to HRP-412 CHECKLIST: Pregnant Women.
[27] Refer to HRP-415 CHECKLIST: Prisoners
[28] A subject is considered "enrolled" when they consent to be in the study.
[29] Only applicable for multisite studies.
[30] i.e., numbers of subjects excluding screen failures.
[31] Payment for participation is not considered a benefit.
[32] For example, data will be double entered, data will be reviewed by another study team member to ensure accuracy, etc.
[33] If your study is multisite and there are differences in how confidentiality will be maintained by the coordination center and our local site, this should be explained in this section (e.g. local site will have samples that are linked to a person's name, but the coordination center will only receive coded samples without any links). Confidentiality regarding use of Social Media will be explained in a protocol section below.
[34] Applicable for studies that present more than minimal risk.
[35] Include information about who (describe in terms of role or group) will review the data.
[36] This should be specific to the social media you are using for the research.
[37] All communications that are directed towards subjects and specific to a particular study will require prior IRB review and approval. All non-IRB reviewable communications can be described in general terms by category – news stories, relevant publications – and representative examples of each can be provided.
[38] Applicable if the research involves more than minimal risk to subjects. If minimal risk, this section is N/A.
[39] If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) those methods should also be described here.
[40] "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.
[41] For example: medical records, CIS, clinical databases, other study records. If the study will access PHI for recruitment purposes without prior authorization from subjects, please address this in the HIPAA Authorization section below.

[42] Attach copies of these documents to the Recruitment Materials section of the study SmartForm. For printed advertisements, attach the final copy. For online advertisements, attach the final screen shots (including any images). When advertisements are taped for broadcast, send the final audio/video tape to IRB@seattlechildrens.org. You may attach the wording of the advertisement to the SmartForm prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.
[43] "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.
[44] This section describes the way(s) in which the processes for this study will not follow Seattle Children's SOP.
[45] See HRP-090, HRP-091, and Investigator Manual HRP-103 for more information.
[46] Note the Short Form Consent may only be used when certain conditions are met. See HRP-091 for requirements for Short Form consent form use.
[47] Seattle Children's IRB prohibits the exclusion of non-English speaking populations from research unless there is sufficient justification for the exclusion. See Investigator Manual HRP-103 for more information.
[48] For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children." The age of majority in Washington is 18; however, sometimes younger children have ability to consent for certain types of care (e.g. sexual reproduction/health; mental health; drug/alcohol treatment). For research conducted outside of the state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." If the sites in other states in the study are conducting their own IRB review, you do not need to worry about this--type N/A. If you are conducting research and are actively recruiting participants outside of Washington who are NOT coming to SCH to give consent and who will be covered under SCH IRB approval, this section should be addressed in your protocol.
[49] For minimal risk studies and greater than minimal risk studies that offer a prospect of benefit, the IRB generally requires one parent to provide permission for the child to participate.
[50] If parental permission will not be obtained, please address this in the Waiver or Alteration of Consent Process below.
[51] See HRP-013 for more information.
[52] The IRB generally follows the following guidelines for written assent: children 7-12 should provide written assent on the "simple" assent form (HRP-502G); children 13-17 should provide written assent by co-signing the parental permission form (HRP-502A). The IRB will consider other assent scenarios (e.g. verbal assent for some or all children; not requiring assent for some or all children; or waiving assent): please provide details about the plan for your study. See HRP-090 and HRP-416 for more information on waiving assent and when assent is not necessary.
[53] See Appendix A-13 of the Investigator Manual HRP-103 for requirements for re-consent at age 18. If you think you meet the conditions for a waiver at 18, please address this in the Waiver or Alteration of Consent Process below.
[54] See "HRP-417 Cognitively Impaired Adults" for further information.
[55] For example: durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child. If you are following HRP-013 in order to make this determination, simply state that in this section. For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." If the sites in other states in the study are conducting their own IRB review, you do not need to worry about this--type N/A. If you are conducting research and are actively recruiting participants outside of Washington who are NOT coming to Washington to give consent and who will be covered under SCH IRB approval, this section should be addressed in your protocol.
[56] The IRB may allow the person obtaining assent to document assent on the consent document.
[57] For example: consent/parental permission will not be obtained, required information will not be disclosed, the research involves deception, waiver for participants who turn 18, waiver for information collected about a non-present parent, or other waivers as necessary.
[58] The IRB needs to make all the waiver findings and key to this determination is that the IRB understand why it is not practicable to do the research without a waiver of consent. You need to provide a rationale in order for the IRB to consider whether the waiver criteria are met. See "HRP-410: Waiver or Alteration of the Consent Process" for further information.
[59] Possible reasons might include: a) you are not collecting information that could put subjects or their families at harm, e.g., affect eligibility for insurance, employability, stigmatization; b) you are not collecting information that would alter or affect the subject's care; c) any publication or presentation of research results would be done in a manner that would never reveal an individual's identity either directly or indirectly.
[60] Possible reasons could be: a) inability to locate families because of the lengthy time period over which the records/samples were created; b) many of the subjects whose records, data, or specimens will be used may have died and contacting the families about the research could cause harm and anguish to families; c) all eligible patients must be included in the study for the results to be meaningful.
[61] See "HRP 419: Waiver of Consent for Emergency Research" for further information.
[62] This section describes the ways in which the procedures will not be following Seattle Children's SOP.
[63] See "HRP-411: Waiver or Written Documentation of Informed Consent" for further information.
[64] An information sheet template can be found in the Click IRB Library and should be attached to the consent form of the study SmartForm. For internet research, the information sheet can be translated to an on-line format, if desired.
[65] The IRB sometimes requires a script if you are having the consent conversation over the phone rather than in person. Templates for a consent script are available on the IRB website on the Participant Recruitment page and should be attached to the study SmartForm.
[66] PHI is health information that is also identifiable because it includes one or more of the 18 HIPAA identifiers. See Investigator Manual HRP-103 for the list of HIPAA identifiers.
[67] If your study involves using or creating PHI and your only contact with participants is online, you can request an alteration of HIPAA authorization to remove the signature requirement. As an alternative to a waiver of documentation of consent and an alteration of HIPAA authorization, you must demonstrate that the electronic consent signatures are compliant with applicable state/international law (in Washington, see RCW 19.34.300).
[68] For example: altering HIPAA elements for international research.
[69] Possible reason could be: the nature of the research is specific to individuals' health and requires access to individuals' health records.
[70] See "HRP-316: Payments" for further information.
[71] Methods of payment include check, ClinCard, gift cards, etc. Provide details on who will be the recipient of the payment (parent or child).
[72] Reimbursement is used when the subject is paid back for travel expenses such as transportation, food, childcare, or lodging. Reimbursement is generally distributed to person who incurred cost (usually parent) and requires receipts to be submitted.
[73] This could include things like fuel/transportation costs, parking, and/or childcare.
[74] Type N/A if this section does not apply.

[75] Provide enough information to convince the IRB that the principal and/or co-investigator(s) are appropriately qualified to conduct and supervise the proposed research. When applicable, describe their prior clinical experience with the test article or study-related procedures, or describe their knowledge of the local study sites, culture, and society.

[76] For example, as appropriate: (1) Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit? (2) Describe the time that you will devote to conducting and completing the research. (3) Describe the facilities in which the research will be conducted. (4) Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research. (5) Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

[77] Including communication between sites of current study document versions and modifications.

[78] See your contract/agreement or Sponsor Documentation if you are unsure