Web-based Cognitive-behavioral Intervention for Pain in Pediatric Acute Recurrent and Chronic Pancreatitis: Protocol of a Multicenter Randomized Controlled Trial from the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)

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Clinical Trial Registration #: NCT03707431

Abstract

Introduction. Abdominal pain is common and is associated with high disease burden and health care costs in pediatric acute recurrent and chronic pancreatitis (ARP/CP). Despite the strong central component of pain in ARP/CP and the efficacy of psychological therapies for other centralized pain syndromes, no studies have evaluated psychological pain interventions in children with ARP/CP. The current trial seeks to 1) evaluate the efficacy of a psychological pain intervention for pediatric ARP/CP, and 2) examine baseline patient-specific genetic, clinical, and psychosocial characteristics that may predict or moderate treatment response. **Methods.** This single-blinded randomized placebo-controlled multicenter trial aims to enroll 260 youth (ages 10-18) with ARP/CP and their parents from twenty-one INSPPIRE (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE)** centers. Participants will be randomly assigned to either a web-based cognitive behavioral pain management intervention (Web-based Management of Adolescent Pain Chronic Pancreatitis; WebMAP; N = 130) or to a web-based pain education program (WebED; N = 130). Assessments will be completed at baseline (T1), immediately after completion of the intervention (T2) and at 6 months post-intervention (T3). The primary study outcome is abdominal pain severity. Secondary outcomes include pain-related disability, pain interference, health-related quality of life, emotional distress, impact of pain, opioid use, and healthcare utilization. **Conclusions.** This is the first clinical trial to evaluate the efficacy of a psychological pain intervention for children with CP for reduction of abdominal pain and improvement of health-related quality of life. Findings will inform delivery of web-based pain management and potentially identify patient-specific biological and psychosocial factors associated with favorable response to therapy.

Keywords: children; chronic pancreatitis; acute recurrent pancreatitis; pain; cognitive-behavioral therapy; internet intervention

Introduction

Abdominal pain occurs in ~80% of children with acute recurrent or chronic pancreatitis (ARP/CP) and is associated with increased disease burden and economic costs [1, 2]. As pain related to pancreatitis becomes more frequent and severe, it can lead to significant decline in children's health and functioning, including frequent missed school days, emergency room visits and recurrent hospitalizations [3, 4], and greater exposure to opioids [5]. Moreover, pain associated with pediatric ARP/CP may continue into adulthood, often with worsening disease and reduced quality of life [6, 7]. Pain related to ARP/CP is hypothesized to have a multifactorial etiology with evidence of a strong central component of pain [8]. Traditionally, pain in pediatric CP has been treated through medical procedures, surgery, and opioids, but unfortunately. medical therapies have demonstrated limited efficacy for reducing pain [9].

Surprisingly limited attention has been directed toward evaluating the efficacy of non-pharmacological pain interventions for children with ARP/CP, as reflected by the absence of published RCTs. Psychological intervention for pain may be a particularly promising treatment avenue for this population, as it addresses psychosocial issues (e.g., negative mood, sleep problems) that are associated with centralized pain. In other populations of youth with chronic abdominal pain, psychological interventions using cognitive-behavioral therapy (CBT) have demonstrated efficacy in reducing pain symptoms, pain-related disability and emotional distress [10]. Moreover, delivering psychological interventions during childhood may present a unique opportunity to teach patients lifelong self-management skills and preemptively reduce the enormous impact of chronic pain, disability, and opioid dependency in adulthood as youth grow older [10, 11].

We are delivering CBT via the Internet to overcome the primary barriers that prevent children from receiving psychological intervention (i.e., geographic distance from treatment centers and the limited availability of psychological expertise) thus increasing accessibility [11]. Our research team has made significant progress in the development and evaluation of a web-based CBT intervention for chronic pain, Web-based Management of Adolescent Pain (WebMAP), which has shown improvements in pain and disability outcomes comparable to conventional office-based CBT in youth with a variety of chronic pain conditions, including abdominal pain [12]. Following cognitive-behavioral, family systems, and social learning frameworks, the WebMAP program includes separate interventions for adolescents and their parents which target maladaptive cognitions and negative mood, problems with sleep, behavioral activation, and interpersonal behaviors. In this study, we adapted and tailored the WebMAP program for children and adolescents with pain related to ARP/CP.

Moreover, identification of individual characteristics including psychosocial and genetic risk factors that increase or decrease treatment response can guide treatment-by-patient matching and advance the goal of personalized pain treatment in this population. Guiding the selection of treatment response moderators, developmental models of pediatric pain impact have identified child emotional factors (depression and anxiety) and family factors (family functioning) as strong predictors of chronic pain and pain-related disability in children [13, 14]. However, it not known whether these psychosocial factors predict better (or worse) response to treatment in pediatric ARP/CP. Additionally, while smoking and alcohol consumption are the major risk factors for CP in adults, genetic risk variants are strongly associated with ARP/CP in children and genetic testing is an integral part of evaluation. Thus, children comprise an excellent group

to evaluate whether (and which) genetic factors, in combination with psychosocial characteristics, may predict response to CBT pain treatment.

Here we report the methodology of the first RCT of a psychological intervention to treat pain in pediatric ARP/CP. The primary goal of this randomized, single-blinded, placebo-controlled trial is to determine the efficacy of web-based CBT (WebMAP) compared to web-based education (WebED) in the largest cohort of well-phenotyped children with ARP/CP (INSPPIRE: INternational Study Group of Pediatric Pancreatitis: In search for a cuRE) [15]. Our secondary aims are to identify treatment response moderators; specifically, we will evaluate individual-level genetic and psychosocial characteristics associated with better (or worse) treatment response to WebMAP.

Methods

Participants and setting

The clinical trial is registered and available at Clinicaltrials.gov (NCT03707431). The study sample will include 260 children and adolescents ages 10-18 years with ARP or CP and one of their parents (or caregivers). Eligible participants will have received a diagnosis of ARP or CP from one of 21 centers participating in the INSPPIRE 2 Cohort study [15]. See Table 1 for a complete list of study eligibility criteria. Eligibility criteria are based on the INSPPIRE 2 definition of ARP and CP [15] and a pain frequency that allows for delivery of a relevant treatment to youth experiencing frequent pain as well as detection of improvement within the study period. All 21 centers have been invited to participate and to date 16 centers have approval to refer participants to the study.

Recruitment and enrollment.

Providers at participating INSPPIRE 2 sites will approach eligible children and families and provide them with a study flyer. If the family is interested and willing to participate, the provider will securely send their contact information to study staff via REDCap (Research Electronic Data Capture, Vanderbilt University) [16], email, fax, phone call, or voice message. Study staff will contact families within one business day of receiving the referral to assess eligibility and interest. At some participating sites as directed by their local Institutional Review Board (IRB), interested families will instead contact study staff directly after receiving the study flyer using a toll-free number or email address. Study staff blinded to the randomization schedule will obtain parent consent and child assent for study participation via electronic signature. Study staff will interact with participants weekly throughout the study and document missed time points and dropouts in a local tracking database. Reasons for withdrawal will be documented.

Trial design and randomization.

This study will utilize a single-blinded, randomized parallel group design. Assessments will be completed through the secure, web-based application REDCap [16] at baseline before randomization, immediately after the 8- to 12-week WebMAP intervention, and 6 months after intervention completion. The 6-month follow-up assessment will provide data on durability of treatment effects. Children and parents will complete their surveys independently. After completing the pre-treatment assessment, participants will be randomized to treatment condition: Group A, internet-delivered CBT (WebMAP) or Group B, internet-delivered pain education (WebED). **Figure 1** summarizes the study design.

Randomization will be implemented using a computer-generated randomization schedule to derive a group assignment for each ID number. Randomization will be blocked in sets of four. The randomization schedule will be stored in a password-protected Excel spreadsheet. To ensure

that study staff who perform the intervention assignment are blinded to the randomized allocation sequences, each participant's group assignment will be revealed only after the participant completes the pre-treatment assessment. Participants will not be informed whether they are receiving an active or control treatment, however, they may be able to determine which group they are in based on the contents of the web program. All outcome measures will be completed online by study participants, further reducing the risk of bias.

Intervention procedures.

Patients assigned to the experimental arm of the study will receive access to the WebMAP program as previously described, [12] receiving internet-delivered CBT over an 8-12-week intervention period. The control group will receive access to a pain education control web site for the same length of time (WebED). Both are password-protected web programs with separate child and parent versions. All study-related interventions will be adjunctive to patient care provided by their primary pediatric gastroenterologist. Although the treatment interventions are self-guided, study staff will have frequent interactions with participants (1-2 times weekly) during the treatment period for the purposes of monitoring program completion and for communicating with participants to evaluate any unwanted treatment reactions or adverse events.

Internet cognitive-behavioral therapy condition (WebMAP). The program design and treatment content of WebMAP follow cognitive-behavioral, social learning, and family systems' frameworks. This interactive, travel-themed program teaches relaxation skills, pain coping strategies, parent behavioral techniques, and parent communication methods. Because the original program was developed for children with a range of chronic pain conditions, we made several adaptations to tailor the program for pediatric ARP/CP. Based on qualitative feedback from children with ARP/CP and their parents, we integrated several patient video and vignette

examples of the impact of pain and application of skills for children with ARP/CP and their families. We also adapted the first educational module of WebMAP to focus specifically on pain related to pancreatitis.

The eight child treatment modules include: 1) education about pancreatitis related pain, 2) recognizing stress and negative emotions, 3) relaxation strategies (e.g., imagery, deep breathing, progressive muscle relaxation), 4) implementing coping skills at school, 5) cognitive skills (e.g., recognizing and reducing negative thoughts), 6) lifestyle interventions (e.g., sleep habits, diet), 7) staying active (e.g., activity pacing), and 8) relapse prevention.

The eight parent treatment modules are: 1) education about pancreatitis related pain, 2) recognizing stress and negative emotions, 3) behavioral strategies to increase their teen's positive coping (e.g., attention and praise), 4) implementing strategies to support school goals, 5) modeling positive coping strategies, 6) sleep and lifestyle interventions, 7) family communication, and 8) relapse prevention. Each parent and child module takes approximately 20 minutes to complete.

The WebMAP program includes vignettes, videos of children with ARP/CP and their parents, illustrations, and reinforcing activities used throughout the program to increase interactivity. Children and parents identify personal goals and enter information, allowing for personalization of information for weekly behavioral assignments. Analogous to in-office CBT, children and parents are asked to complete 1 module per week and spend time practicing skills/completing assignments in 6 of the 8 modules. The following general structure is used in each module: summary of skills and educational material to be learned, rationale for why this information is important, main content, interactive quizzes (in game format with feedback), and an assignment screen presenting information for carrying out a specific skill over the coming

week. Completion of quizzes and assignments allow investigators to understand knowledge acquisition and retention of treatment content.

Assignment completion. As in in-office CBT, assignments focus on practice and acquisition of skills taught within each weekly teen and parent module. For each assignment, participants are asked to report on the frequency of use, level of ease, and helpfulness of each skill. Participants are then provided with personalized feedback based on these responses. Personalized feedback includes a summary of progress, feedback on skills practice, strategies to overcome barriers to using skills, and encouragement to continue to use the program. Assignment completion is a requisite before teens and parents proceed to the subsequent module.

Internet pain education condition (WebED). The education control condition serves as an attention control condition to equalize time, attention, and computer usage by providing relevant information about chronic pain**.** The program contains 8 modules with information compiled from publicly available educational websites about chronic pain (e.g., WebMD, AboutKidsHealth, National Pancreas Foundation). We developed additional educational content about pain and symptoms in ARP/CP to be relevant and credible for these children and their parents. The control version does not include any instruction on the behavioral and cognitive skills taught within the WebMAP program. Children and parents are instructed to log in and read one education module per week for approximately 20 minutes (the same interval as the CBT group). In our prior RCTs that have used a pain education control website, parents and children have shown a high level of engagement and high ratings of treatment credibility [12].

Treatment fidelity. The administrative interface of the web program has a tracking system in place for recording each time a user logs in or completes a module, allowing measurement of web site usage. All completed data fields within modules are stored (e.g.,

completion of quizzes, assignments), generating a comprehensive activity record of each individual's program usage and their acquisition of skills and knowledge within the program.

Measures.

Covariates. Participant demographic information (age, sex, race, ethnicity, income, occupation, marital status) will be collected via parent report at baseline.

Treatment expectancies. After randomization, youth and their parents will complete a baseline measure of treatment expectancies [17]. This 10-item questionnaire asks youth and their parents to rate the likelihood that Internet pain treatment will lead to symptom improvement on 5-point rating scales (0 = not at all likely, 4 = extremely likely). Higher scores on this measure indicate more positive treatment expectancies.

Primary outcome: Abdominal pain. The Abdominal Pain Index (API) will be used to measure abdominal pain severity at all three time points. The API yields a composite score for pain severity derived from child- and parent-report on pain frequency, duration, and intensity over the prior two weeks. The API is a validated measure of abdominal pain severity that contains four (parent version) or five items (child version) [18].

Secondary outcomes.

Pain-related disability. Child report on the Child Activity Limitations Interview (CALI-9), diary version will be used to assess pain-related disability at each time point. The CALI-9 is a validated instrument that assesses perceived difficulty in completing standard daily physical, social, and recreational activities due to pain [19]. Each of the 9 items is scored on a 6-point scale, with higher scores indicating greater pain-related disability. Children complete the diary daily for 7 days at each of the three time points.

Anxiety and depression. Child report on the PROMIS Pediatric Emotional Distress Scales will be used to assess symptoms of anxiety and depression at all three time points. The PROMIS Pediatric Emotional Distress Scales is a validated instrument that includes an 8-item scale of anxiety symptoms (fear, worry, hyperarousal) and an 8-item scale of depressive symptoms [20]. Raw scores from each scale are converted to T-scores, with a distribution mean of 50 (SD ± 10).

Self-efficacy. The Child Self-Efficacy Scale will be used to assess child participants' perceived ability to complete various activities while they are in pain (e.g., *How sure are you that you can make it through a day of school with pain?*) [21]. Each item is scored on a 5-point scale, with higher numbers indicating lower self-efficacy (i.e., 1 = very sure to 5 = very unsure).

Pain interference. Child report on the PROMIS Pain Interference Scale will be used to assess how much pain hinders participation in various social, recreational, cognitive, and physical activities [22]. This scale consists of 8 items, each item scored on a 5-point scale. Higher ratings indicate greater pain-related interference.

Parent impact. Parent report on the Bath Adolescent Pain – Parental Impact Questionnaire (BAP-PIQ) will be used to assess family functioning and emotional impact associated with parenting a child with chronic pain [23]. Each item on the BAP-PIQ is scored on a 5-point scale with higher scores indicating greater impairment.

Health-related quality of life. The Pediatric Quality of Life Inventory (PedsQL) will be used to assess health-related quality of life (HRQOL) via child and parent report at all three time points [24]. Each of the 23 items is scored on a 5-point scale. Higher scores indicate better physical, emotional, social, and school functioning.

Health care use. The Client Service Receipt Inventory (CSRI) [25] will be used to assess health care use at baseline and 6 month follow up. The CSRI has been adapted for adolescents with chronic pain [26] and subsequently used in pediatric pain populations [27]. In this survey, parents report on all health service use (e.g., hospitalizations, outpatient health care visits) including medication usage (including opioid and non-opioid medications) during the previous 9 months.

Treatment satisfaction. The Treatment Evaluation Inventory [25] – Short Form (TEI) will be used to assess treatment satisfaction via child and parent report at post-treatment and follow-up [28]. The TEI assesses acceptability and satisfaction with a treatment program.

Treatment experiences. Any unwanted experiences during treatment will be collected at post-treatment and follow-up using child and parent report on a self-report scale developed for this study that asks participants about any negative changes in stress, anxiety, or pain symptoms due to study participation.

Predictors/Moderators.

Clinical and genetic variables. We will include baseline information collected from the INSPPIRE 2 study, including clinician report of history and symptoms, and a blood draw for testing subjects' ARP/CP genetic variants. We will analyze 79 complete genes and 141 additional targets. Genetic susceptibility is the major driving factor for the onset of ARP/CP in children and genetic testing is an integral part of the evaluation. Consequently, our genetic screen will cover Mendelian disorders of the exocrine pancreas including: cystic fibrosis, CFTR-related disorders, Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, hereditary pancreatitis, and Maturity-onset diabetes of the young (CEL, MODY8). See Table 3 for a list of

genetic variables. Each of these genetic variants has the potential to influence development of pain, the pattern of pain, and the response to therapy.

Baseline demographic and psychosocial variables. We will test several possible baseline demographic and individual child moderators that may have an impact on the intervention effect. This will include child age and sex, and psychosocial variables (i.e., baseline anxiety and depression on the PROMIS Pediatric Emotional Distress Scales [20].

Sample Size and Power Calculations

We based power calculations on expected differences in the primary outcome (API) derived from our previous trials of WebMAP. The estimate of the standard deviation of API is approximately 0.85. We expect a difference of 0.30 between WebMAP and WebED in the mean score of abdominal pain severity at 6-month follow-up, corresponding to a small effect size (Cohen's d approximately = .30 - .35). At the significance level of 0.05, a sample size of 115 subjects per group is required to have 80% power to detect this difference. Taking into account 10-15% attrition, we will therefore plan to enroll 130 patients per group. The power calculation for the secondary aim is based on correlation coefficient. Given the sample size of 115 subjects in the treatment group, we have 80% power to detect the correlation of 0.27 between gene (or baseline clinical characteristics) and API, at the significance level of 0.05. As the LMM is more efficient and is an intent-to-treat approach that will use data from the full sample, the actual power will be greater.

Data Analysis

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 self-report measures. The analysis will be an intent-to-treat analysis including all randomized subjects.

Analytic Plan: Treatment efficacy. LMM and GLMM will be used to compare the change in the primary and secondary outcomes over time (from baseline to follow-ups) between WebMAP and WebED. These models will include time, treatment condition (1 = CBT condition; 0 = Education condition), and their interaction (i.e., time X treatment condition). We will include demographic and clinical factors as needed to adjust for potential confounding effects. For categorical variables, the generalized linear mixed model (GLMM) will be used to compare the changes over time (from baseline to follow-ups) between WebMAP and WebEd.

Analytic Plan: Moderators of treatment response. Linear mixed models (LMM) will be used to evaluate individual genetic, clinical, (e.g., demographics, age at diagnosis, ARP or CP diagnosis, number of pancreatitis attacks) and psychosocial characteristics (e.g., child anxiety, child depression, and family functioning) as general predictors and moderators of treatment response. Repeated measures of abdominal pain severity and health-related quality of life in the CBT group will serve as the outcome variables. These models will comprise the following variables: (1) intercept and Time (i.e., the slope terms); (2) individual characteristics that were used to predict the intercept (pre-treatment score) and slopes of improvement (i.e., individual characteristic X time) and (3) potential predictor/moderator variables, treatment condition, and their interaction (i.e., individual characteristic X treatment X time).

Following the data analytic approach advocated by Kraemer et al [29], individual characteristics will be considered moderators if they predict a better (or worse) response to the

treatment condition compared to the control condition. *Moderator* variables will require evidence of a significant interaction between the predictor (individual characteristic), study treatment condition (dichotomized: 0 = Internet CBT; 1 = Internet Education), and time (i.e., individual characteristic X treatment X time). Thus, a significant predictor X treatment X time interaction indicates that the trajectory of treatment response differs across the treatment conditions and depends on the level of the moderator variable. On the other hand, *general predictors* are individual characteristics associated with treatment outcome irrespective of study condition (i.e., across both conditions); thus there is evidence of a significant interaction with time point (i.e., Individual characteristic X Time) but no significant interaction with treatment condition.

To investigate multiple genetic, clinical, and psychosocial individual characteristics as moderators, we will first conduct univariate analysis by independently testing the effects of each individual characteristic on the abdominal pain severity outcome to see if there is reasonable signal of whether they will have a significant effect on the rate of symptomatic improvement using a p-value threshold of <.10. Using this procedure, only those individual characteristics that had a significant interaction with time at the p-value < .10 level in univariate analysis will be included in a final multivariate model. If the number of putative general predictors/moderators included in the final multivariate model is still large, model selection (e.g., using LASSO) will be performed to obtain a parsimonious model that could identify characteristics that significantly moderate treatment outcomes. Further analysis utilizing machine learning programs for cluster analysis, such as principle component analysis, will be conducted as complementary and confirmatory analyses.

For models testing genetic polymorphisms that predict treatment response, in the initial evaluation, “genetic signatures” will be used as covariates. 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 moderators (i.e., will only be evaluated in univariate analyses and not in a final multivariate model).

Discussion

Abdominal pain is highly prevalent in children with ARP and CP [7] and is associated with negative impact on multiple domains of physical, psychological, and social functioning[7, 30]. Given that the burden of pain worsens with age, early implementation of therapies during childhood are critically important for reducing opioid dependency and preventing functional impairments that develop with advanced disease in adulthood [31]. Currently, effective non-pharmacological pain interventions do not exist for pediatric ARP/CP. In this paper, we report the methodology of the first NIH-funded randomized multicenter clinical trial to test the efficacy of an internet-delivered psychological intervention in a large pediatric ARP/CP cohort.

The results of this trial will have important implications for pain management in children with ARP/CP and their families by understanding whether a psychological self-management approach to chronic pain symptoms can reduce pain and improve quality of life. This study represents a significant advance in pediatric pancreatology as it is the first to introduce a psychological pain management option for this population, that may represent a new model of treatment in ARP/CP. This trial will also examine whether any genetic, clinical, and psychosocial characteristics predict or moderate treatment response, further expanding our

understanding of this disease and enabling precision medicine approaches. Specifically, we will be able to identify whether patient-specific clinical and psychosocial factors are associated with improved response to web-based CBT. In addition, our internet-delivered program is a cost-effective alternative to in-office CBT that may increase accessibility and diminish socioeconomic or geographic disparities in care.

In summary, the results of this trial are expected to provide information on the main and moderating effects of a web-based psychological pain management program for pediatric ARP/CP. If successful, the intervention has potential for widespread dissemination to children with ARP/CP at treatment centers around the world.

Figure 1. CONSORT diagram depicting participant flow.]

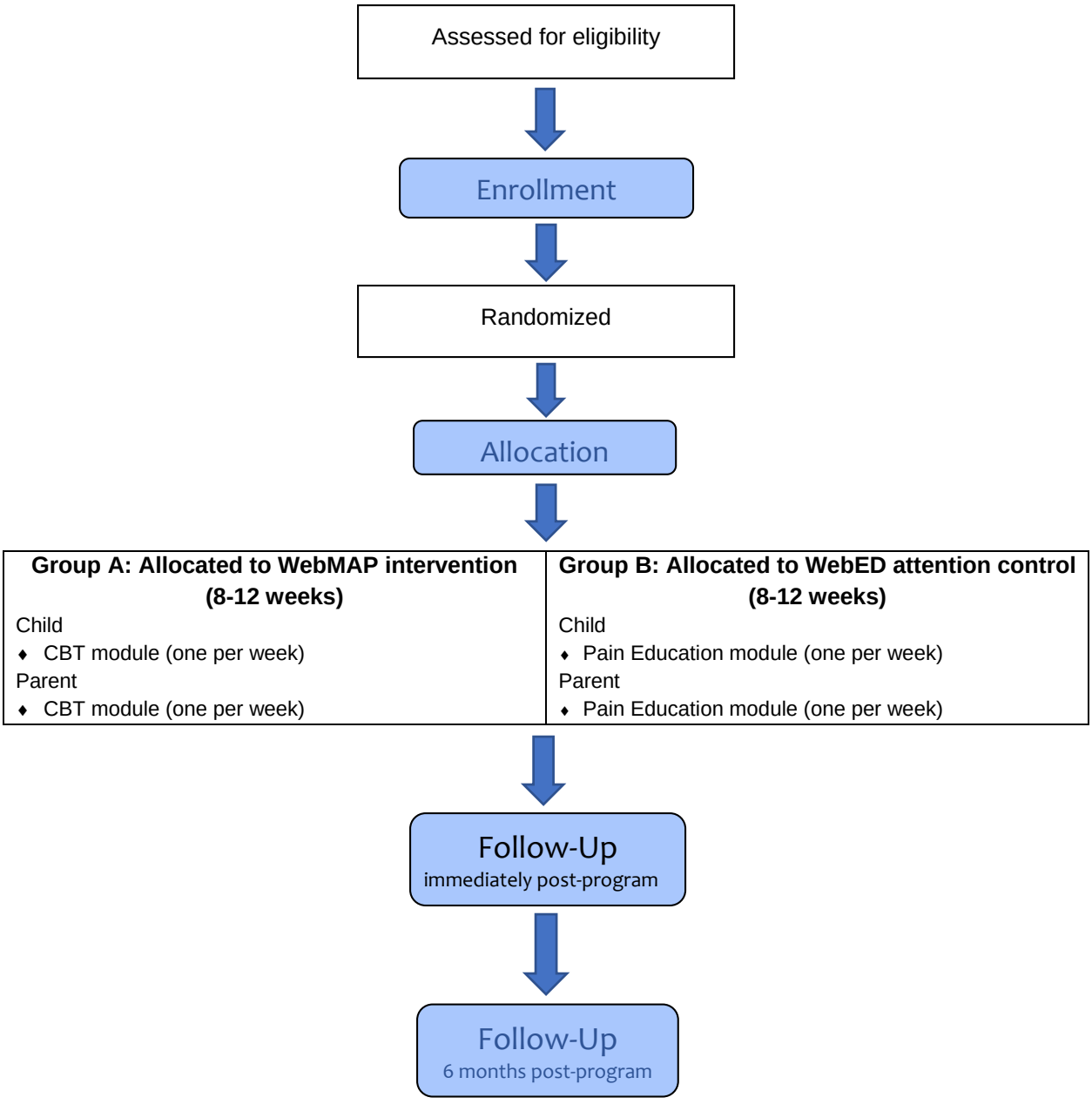

Table 1. Study eligibility criteria

Inclusion Criteria
• Child diagnosed with chronic or acute recurring pancreatitis • Child age is between 10-18 years • Child abdominal pain frequency > once/month for at least 3 months • Child and parent have access to the Internet on any web-enabled device
Exclusion Criteria
• Child or parent is unable to read/write or speak English • Child is unable to read at the 5th grade level due to learning or developmental delays • Child has cystic fibrosis • Child has Shwachman-Bodian-Diamond Syndrome • Child diagnosed with acute pancreatitis with no evidence of chronic or persistent abdominal pain • Child has anticipated surgery (TPIAT or other) during study participation (6-month time frame) • Child had recent surgery (TPIAT or other) within the past thirty days (or longer if still in acute recovery period)

Table 2. Study measures

Measure	Description of measure	Respondent	Time point administered		
			T1	T2	T3
Demographic and clinical measures					
Background Questionnaire	Obtain demographic and socioeconomic information including age, sex, gender, race, ethnicity, family income, occupation, and marital status.	Parent	✓		
Treatment expectancies	Rate expectations that the program will be useful and helpful.	Child, Parent	✓		
Primary outcome measures					
Abdominal Pain Index (API)	Assess abdominal pain intensity, duration, and frequency during the previous 2 weeks.	Child, Parent	✓	✓	✓
Secondary outcome measures					
Child Activity Limitation Interview (CALI-9)	9-item measure used to assess daily pain-related disability related to limitations in common activities for 7 days in a pain diary.	Child	✓	✓	✓
PROMIS Pediatric Emotional Distress Scales	Includes 8-item scale of anxiety (fear, worry, hyperarousal) and 8-item scale of depressive symptoms.	Child	✓	✓	✓
Child Self-Efficacy Scale	7-item measure used to assess perceived ability to complete certain activities when in pain.	Child	✓	✓	✓

PROMIS Pain Interference Scale	8-item measure used to quantify the degree to which pain restricts engagement in various activities.	Child	✓	✓	✓
Bath Adolescent Pain Questionnaire – Parent Impact	Assess parent perception of burden, family functioning, and emotional distress related to caring for an adolescent with pain.	Parent	✓	✓	✓
Pediatric Quality of Life Inventory	Assess physical, emotional, social, and scholastic functioning via child self-report and parent-proxy report.	Child, Parent	✓	✓	✓
Health Care Use Survey	Report use of various health care services such as clinic visits, emergency visits, and opioid and non-opioid medications, as well as health-related impacts during the previous 9 months.	Parent	✓		✓
Treatment Evaluation Inventory – Short Form	Assess treatment satisfaction and acceptability	Child, Parent		✓	✓
Treatment Experience Questionnaire	Report unwanted effects of study participation on stress, anxiety, and pain symptoms.	Child, Parent		✓	✓
Clinical Information (from INSPPIRE2 Study)	Includes clinician report of pancreatitis treatment history, and blood draw for testing CP genetic variants.	Clinician, Child	✓		

Table 3. Genetic variables

Primary ARP/CP susceptibility genes:	Description
CASR	Calcium-sensing Receptor
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
SBDS	Shwachman-Bodian-Diamond Syndrome Ribosome Maturation Factor
SBDSP	Shwachman-Bodian-Diamond Syndrome Pseudogene
SPINK1	Serine Peptidase Inhibitor, Kazal Type 1
CEL	Carboxyl Ester Lipase
CELP	Carboxyl Ester Lipase Pseudogene
CPA1	Carboxypeptidase A1
CLDN1 – key SNPs	Claudin 1 (key single nucleotide polymorphisms)
PRSS1	Serine Protease 1
PRSS2	Serine Protease 2
PRSS3	Serine Protease 3
PRSS1-2 locus	Serine Protease 1-2 locus
GGT1	Gamma-Glutamyltransferase 1
Lipid metabolizing genes associated with hypertriglyceridemia and ARP:	
APOA5	Apolipoprotein A5
APOC2	Apolipoprotein C2
FABP	Fatty Acid Binding Protein
LPL	Lipoprotein Lipase
Inflammation severity variants:	
IL10	Interleukin 10
IL22	Interleukin 222
IL22RA1	Interleukin 22 Receptor Subunit Alpha 1
IL22RA2	Interleukin 22 Receptor Subunit Alpha 2
IL23R	Interleukin 23 Receptor
Drug metabolism and pain management genes:	
COMT	Catechol-O-Methyltransferase
HTR2A	5-Hydroxytryptamine Receptor 2A
CYP2C19	Cytochrome P450 Family 2 Subfamily C Member 19
CYP2D6	Cytochrome P450 Family 2 Subfamily D Member 6
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
CYP3A5	Cytochrome P450 Family 3 Subfamily A Member 5
OPRD1	Opioid Receptor Delta 1
OPRM1	Opioid Receptor Mu 1

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