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Title

Digital cognitive-behavioral therapy for pain management in individuals with recurrent acute and chronic pancreatitis (IMPACT-2): study protocol for a hybrid effectiveness-implementation trial

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Abstract

Background: Abdominal pain is a cardinal symptom of pancreatitis, present in up to 90% of patients with recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP). Increases in pain severity and constancy are associated with significant morbidity including depression and anxiety symptoms, low physical functioning, sleep disturbance, and low quality of life, as well as high economic and societal burden. Our pilot study of digital cognitive-behavioral therapy (CBT) demonstrated preliminary efficacy in improving pain and disability in adults with recurrent acute and chronic pancreatitis pain. Building on these promising findings, this hybrid effectiveness-implementation clinical trial seeks to test the effectiveness of digital CBT in a large sample and to gather data on future implementation of this scalable intervention.

Methods: This multisite, pragmatic clinical trial is recruiting 280 adults (ages 18+) with recurrent acute or chronic pancreatitis who report chronic pain. Participants are randomized 1:1 respectively to one of two groups: 1) Digital CBT, providing access to the Pancreatitis Pain Course to learn pain self-management skills (e.g., relaxation, activity pacing, goal setting), or 2) Digital Pain Education (access to education website about pancreatitis pain). Evaluations are completed at baseline, two months, and six months follow up. This study leverages resources of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC), a NIH-sponsored U01 consortium, with recruitment from their nine clinical centers and from self-referral in the community through partnerships with community-based and clinical organizations. Relevant stakeholder groups (patients, providers, organizational managers) will participate in a process evaluation to inform future implementation in clinic and community settings. Primary effectiveness outcomes are pain interference and severity. Secondary outcomes include opioid use, depression, anxiety, quality of life and sleep.

Discussion: Findings from the IMPACT-2 trial will significantly advance solutions for non-pharmacological pain management in RAP and CP. If successful, our project will address a critical need for low-cost, accessible pain self-management.

Trial registration: NCT06386224, https://www.clinicaltrials.gov/study/NCT06386224; first posted: 04-26-2024

Keywords

Recurrent acute pancreatitis, Chronic pancreatitis, pain management, cognitive-behavioral therapy, digital intervention, randomized controlled trial

Administrative information

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Role of sponsor {5c}	TMP and DC devised the study objectives and design. TMP led the writing of this manuscript. DY, BD, AD, and CZ contributed to the conception of the study and the development of the proposal. All authors have provided edits, reviewed, and approved the final manuscript.

Introduction

Background and rationale {6a}

Acute pancreatitis is among the leading cause of hospitalizations for acute gastrointestinal disorders, with abdominal pain as a primary symptom associated with high morbidity, and reduced health-related quality of life (HRQL).[1–3] Pancreatitis exists on a mechanistic spectrum,[4] and an acute episode can lead to recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP), both of which substantially increase the risk for pancreatic cancer.[5] Nonspecific, epigastric abdominal pain is often the first presentation and is the leading symptom prompting medical care. Present in 65-90% of patients with RAP and CP,[6] repeated events of severe abdominal pain are associated with long-term reduction of HRQL across multiple domains of physical, psychological, and social functioning,[7,8] and may result in disability and increased health resource utilization.[9] In all its forms, pancreatitis costs the United States more than $2 billion per year in healthcare spending.[10]

Abdominal pain is a common and distressing symptom for patients with RAP and CP.[6] The pain may vary in its temporal nature and severity, with some patients experiencing episodic high intensity pain, prolonged periods of unremitting pain, or both.[6] Cohort studies have found significant associations between pain severity and greater use of opioids and lower HRQL.[11,12] In our own recent study from the PROCEED cohort of 488 participants with CP, we found that severe or constant pain was independently associated with significant decrements in physical, mental, and social health and greater prevalence of moderate to severe symptoms of depression, anxiety, sleep disturbance and low physical function.[13] Pain-associated psychological comorbidities are common; for example, in one recent study of patients with CP, 40% had clinically significant levels of anxiety and depressive symptoms, which were associated with higher pain severity and pain interference.[14] Furthermore, substance use, in particular alcohol abuse and smoking, are the most commonly recognized causes of RAP and CP[15] and are associated with increased pain interference and burden in general chronic pain populations.[16,17] Furthermore, there is evidence that non opioid, integrative and complementary health practices may be beneficial in chronic pain,

including chronic pancreatitis.[18]

Pain management is clinically challenging, and remains a top priority of patients with CP. Non-opioid treatment strategies for abdominal pain are essential to minimize opioid-related side effects and dependency.[19] Given these challenges, recent guidelines encourage the use of psychological interventions as part of a multidisciplinary approach to more effectively manage painful CP.[20] Psychological therapy, and the principles on which they are based, play an important role in chronic pain self-management. CBT, a non-opioid intervention, equips patients with cognitive and behavioral skills to minimize the impact of their painful condition on activity participation and psychosocial well-being. Indeed, multiple systematic reviews and meta-analyses of CBT for chronic pain have demonstrated beneficial effects on pain, disability, HRQL, and mood in many populations.[21–23] A recent comparative effectiveness trial in a large health system demonstrated benefits of digitally delivered CBT (delivered either via telehealth or self-completed modules online) compared with usual care among individuals with high-impact chronic pain (ref). Given the persistence of pain and the high rate of psychological comorbidities in patients with RAP and CP, CBT could be of significant benefit;[24] however, to date, there are no large-scale trials of CBT in this population.

Many patients lack access to in-person CBT and experience other significant barriers to seeking services, particularly in low-income and rural areas. A viable low-cost strategy for bridging this critical gap in service delivery is to use digital health interventions to teach pain self-management skills. To meet this need, we adapted an evidence-based chronic pain CBT program, the *Pain Course*,[25,26] to be relevant for individuals with RAP and CP pain by tailoring educational material about pancreatitis pain and adapting case vignettes. Our pilot randomized trial of the *Pancreatitis Pain Course* in 30 adults with painful RAP or CP assigned to CBT or wait-list control found that patients randomized to CBT demonstrated a significant reduction in pain severity and pain interference from baseline to posttreatment and three-month follow-up compared to patients in the wait-list control condition.[27]

Objectives {7}

Building from these promising preliminary data, our objectives are to (1) determine the effectiveness of the *Pancreatitis Pain Course* in improving pancreatitis pain outcomes, (2) identify implementation facilitators, challenges, and solutions for structures and processes that contribute to the seamless integration of the *Pancreatitis Pain Course* into clinical centers and the community, and (3) explore the moderating effects of social determinants of health with changes in pain interference and severity following treatment. We hypothesize that individuals with painful RAP or CP who receive digital CBT will experience greater reductions in pain interference and severity (primary outcomes) as well as reduced opioid use, depression and anxiety, and improved quality of life and sleep (secondary outcomes) compared to patients receiving digital pain education control.

Trial design {8}

The IMPACT-2 trial is a hybrid effectiveness-implementation trial type 1 with a two-group parallel arm randomized clinical trial design with randomization in a 1:1 allocation ratio at the individual participant level to two intervention arms (digital CBT or digital Pain Education). This is a superiority trial. The study is registered in ClinicalTrials.gov [NCT06386224] and the protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. **Figure 1** illustrates the study recruitment flow and condition allocation for IMPACT-2.

Methods: Participants, interventions and outcomes

Study setting {9}

The study is being conducted at 16 clinical sites across the United States (to date, Baylor College of Medicine, Cedars-Sinai Medical Center, Dartmouth Hitchcock Medical Center, Emory University Hospital, Indiana University Health, Mayo Clinic, Orlando Health, Stanford University, The Ohio State University Wexner Medical Center, University of Cincinnati, University of Illinois Chicago, University of Florida, University of Kentucky Medical Center, University of Minnesota, University of Pittsburgh Medical Center, and Yale University).

We are also partnering with two community-based organizations that provide supportive services to adults with RAP and CP and their families (to date, National Pancreas Foundation [NPF] and Mission:Cure). The NPF is promoting the study through their social media channels (Twitter, Instagram, Facebook, LinkedIn) and its 130 established Pancreas Centers of Excellence (COEs). Mission:Cure is promoting the study through their clinical trials opportunities page. Seattle Children's Hospital oversees recruitment for all participants from clinics and the community.

Eligibility criteria {10}

Inclusion criteria are (1) age ≥ 18 years, (2) meeting CPDPC criteria for diagnosis of either RAP or CP,[28] (3) willingness to use personal device with internet access (smartphone, computer, iPad) or to borrow a study iPad/hotspot, (4) having experienced moderate pain intensity (rated as 4 or higher on a 0–10 Numerical Rating Scale) in the last month from RAP or CP, and (5) residing in the US or Canada.

CP is defined as having obvious morphological features of CP (i.e., Cambridge 3–4 stage or the presence of pancreatic calcifications on CT scan and/or magnetic resonance cholangiopancreatography, or histological evidence of CP). RAP includes patients who have developed more persistent abdominal pain lasting at least 3 months.

Exclusion criteria are (1) undergoing treatment for cancer, (2) unable to read English well enough to complete questionnaires or read the study website, (3) currently experiencing suicidal ideation, (4) having received endoscopic therapy in the past 30 days, (5) currently receiving treatment from a psychologist (> 4 sessions), (6) received total pancreatectomy, or (7) received pancreatic surgery in the past 90 days. To investigate effectiveness and generate generalizable results, the inclusion criteria are purposefully broad. For patients enrolled from the community, diagnosis of CP or RAP is confirmed by their primary physician or gastroenterologist (using a medical history form developed in our pilot trial).[27]

Who will take informed consent? {26a}

If individuals are interested and eligible to participate, study staff not involved in treatment allocation screen potential participants via phone and obtain verbal consent for study participation. Informed consent is documented electronically using REDCap's eConsent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

N/A: This study does not collect biological specimens, nor is it affiliated with any ancillary studies.

Interventions

Explanation for the choice of comparators {6b}

The IMPACT-2 trial compares digital CBT to digital pain education control to evaluate the effectiveness of this non-pharmacological intervention for pain management in RAP and CP. Education control includes an internet program to control for time, attention, and technology usage by delivering credible pain education from public sources.

Intervention description {11a}

Education control condition (EDU). We developed a website with information about pancreatitis and general principles of pain management and lifestyle factors using content from publicly available educational websites (e.g., National Pancreas Foundation). The program only provides educational content and does not provide instruction in using cognitive-behavioral skills for pain management. In our prior trials using similar EDU control websites, participants have rated education interventions as credible and demonstrated high engagement (module completion rates) and treatment acceptability.[29] Participants randomized to this condition receive access to the EDU program and complete five modules released over the same time interval as the CBT program. Study consent documents refer to both the CBT and EDU programs as "web programs" to blind participants to the intervention being studied.

Cognitive behavioral therapy condition (CBT). Participants randomized to the active CBT intervention arm receive access to the *Pancreatitis Pain Course*, available through any internet-enabled device. The design and treatment content follow a cognitive-behavioral framework in which participants receive information to better understand their CP pain, learn a range of cognitive and behavioral skills to manage their symptoms and difficulties, and practice and adopt the skills taught in the program.[25,26]

The *Pancreatitis Pain Course* is accessed via a secure online login, and all participants are provided their own personal account and password. The program consists of 5 core online lessons, which are in the form of a slide show, and 5 downloadable lesson summaries, which provide homework assignments to assist participants in learning and applying the skills described in the lessons (see **Table 1**). These materials are released over the course of eight weeks (content is metered to allow time for skills acquisition) and include a combination of didactic information and narrative examples. Several detailed case stories and real-world examples of individuals with CP or RAP pain are integrated throughout the course.

Criteria for discontinuing or modifying allocated interventions {11b}

This is a minimal risk behavioral intervention and as such, criteria for discontinuing or modifying allocated interventions do not apply. Subsequent endotherapy or surgery after randomization is documented but patients are not withdrawn from the study. Participants are free to stop participating in the intervention and/or leave the study for any reason at any time. Participants are not removed from the study due to lack of engagement with the intervention and are encouraged to submit assessments at any time points.

Strategies to improve adherence to interventions {11c}

Both arms of the study receive regular reminders to continuously engage with their assigned program. Participants receive email reminders with a direct hyperlink to the program when new modules are available, and additional reminders are sent if modules are not completed within the

designated timeframe. A backend system tracks participants' logins and general use of the *Pancreatitis Pain Course*, including metrics around lesson completions and whether lesson summaries and/or other additional resources were viewed or downloaded. Similar metrics around usage and access of the EDU program components are also available. Study staff use these engagement metrics to conduct additional follow-up with participants as needed.

Relevant concomitant care permitted or prohibited during the trial {11d}

As part of their routine care, all enrolled participants receive usual clinical care at their pancreas or GI clinic, which may include pharmacological and non-pharmacological therapies. Usual care is not be altered for the study in order to enhance generalizability. Initiation of interventions (described in 'Concomitant therapies') is documented during the trial.

Provisions for post-trial care {30}

This is not applicable; there are no provisions for post-trial care because this is a low-risk behavioral intervention trial.

Outcomes {12}

The primary outcomes are changes in pain interference and severity. Secondary outcomes include opioid use, depression and anxiety, quality of life and sleep. Participant outcomes are assessed at baseline, immediate post intervention (8-10 weeks), and at 6-month post-intervention follow-up. The outcome measures are summarized in **Table 2**.

Demographic and Screening Measures

Demographics and social determinants of health. At baseline, participants provide information about their biological sex, gender, race and ethnicity, veteran status, and marital status, along with their pancreatitis history (e.g., onset, cause, past treatments), medications, other medical and psychiatric comorbidities, and surgical history. Participants also complete the Screening for Social Determinants of Health– Short Form (SDOH, American Academy of Family Physicians) to assess

social health risks across the domains of employment, finances, housing, food, transportation, and utilities.

Concomitant therapies. At posttreatment, participants report on ant concomitant therapy received for their pancreatitis, and specifically for pain, including psychosocial treatment, complementary medicine interventions, new medications, endoscopic therapy, surgery, and/or interventional pain management (e.g., celiac plexus blocks) using a checklist.

Substance use screener. Participants complete the Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool (TAPS)[30] at baseline and six-month follow-up. TAPS consists of a four-item screen for the use of tobacco, alcohol, illicit drugs, and the nonmedical use of prescription drugs, followed by a substance-specific assessment of risk level for individuals who screen positive.

Implementation outcomes. To address our second aim, we are conducting semi-structured, open-ended individual interviews with 30 total stakeholders, including 12 patients with RAP or CP, 12 providers, and 6 program managers/organizational leaders. Interview scripts focus on patient and organizational perspectives of the *Pancreatitis Pain Course* and implementation facilitators, challenges, and solutions. Interviews coding is described under the Statistical Analysis section.

Participant timeline {13}

See **Figure 2**. Potential participants are identified either by referral from one of the study's clinical site coordinators or by self-referral through a community or clinical organization. Individuals first complete the study's REDCap eligibility screening tool. Study staff contact the individual to perform additional screening, and if determined to be eligible, they ask the participant for verbal confirmation to participate and direct them to the study REDCap's eConsent platform. Upon provision of written consent, participants are emailed a link to complete their baseline assessments on REDCap. Once the baseline assessment is completed, participants are randomized to one of the two study arms through REDCap and provided with instructions around how to access their

assigned intervention program shortly afterwards. Participants in both arms are expected to complete the programs over 8-10 weeks, although participants continue to have access to their assigned web programs for the full study period. Both groups complete follow-up assessments at 10-weeks and 6-months post-treatment.

Sample size {14}

Our sample size and power consideration are based on detecting small (Cohen's d=0.2) to medium (d=0.5) effect sizes. This is based on our preliminary study using pain and pain interference as primary outcomes, at 80% power and 5% Type I error rate. We assume 15% attrition and, thus, aim to recruit a total of 280 participants. Even with 15% attrition, we will have ~240 patients for analysis. If we have 140/arm in our final analytic sample, then the minimum detectable effect size is 0.34 at 80% power.

Recruitment {15}

Participants are recruited through clinic-based referrals and self-referrals through the community. At participating clinic sites, providers refer potentially eligible patients to the study by providing study information (e.g., study website, study flyer) and asking whether the patient would be willing to be contacted by phone by study staff to undergo additional screening. If patients agree, providers transfer referral information to study staff via a secure, digital study interest form. These patients also can initiate contact with the study staff by directly completing the interest form themselves or by calling the study phone number.

For community-based self-referrals, we are partnering with the National Pancreas Foundation and Mission:Cure using their available channels to promote the study. NPF is largely active on Twitter, Facebook, Instagram, and LinkedIn; they also have a study opportunities webpage and E-newsletter, which is being used to advertise the study. Interested individuals can contact study staff by completing the study interest form or by calling the study phone number.

Assignment of interventions: allocation

Sequence generation {16a}

Computer-generated algorithms produced an allocation sequence table, and this table was uploaded to the REDCap Randomization Module (by a staff member uninvolved with participant contact or data analysis) to facilitate automated randomization. Randomization occurs with equal 1:1 assignment to each study arm, stratified by referral site (clinic or community) and diagnosis (RAP or CP) in blocks of 4.

Concealment mechanism {16b}

Study team members do not upload or have visibility to the allocation table within REDCap, thereby ensuring allocation concealment. Additionally, automated randomization does not occur until after baseline assessments are completed, which prevents any inadvertent visibility into subsequent allocations during time of enrollment.

Implementation {16c}

The allocation sequence table is computer-generated and uploaded directly into the study REDCap Randomization Module. Study staff screen, consent, and enroll participants, and once participants complete their baseline assessments, they are automatically randomized to their study arm via REDCap.

Assignment of interventions: Blinding

Who will be blinded {17a}

Study investigators, outcome assessors, and data analysts are blinded and do not have access to random assignment information. Trial participants may be able to detect that the content of the web program consists of cognitive-behavioral therapy, although consent documents refer to both CBT and EDU interventions as “web programs”. The principal investigators are blinded to the outcome assessments, which are completed independently and remotely by the participants.

Procedure for unblinding if needed {17b}

Study coordinators and statisticians are not blinded to the treatment assignment. In the unlikely

event that an adverse event should occur, unblinding of other study staff can be conducted by the study coordinator who assigns participants to interventions.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All outcome measures are completed online independently by study participants, reducing risk of bias. A detailed overview of the assessments can be found in **Table 1**.

Plans to promote participant retention and complete follow-up {18b}

Participants receive automated survey invitations and reminders at each assessment timepoint. Study staff send additional reminders if assessments are not complete throughout the assessment completion window. We use a database tracking sheet to ensure that all study procedures are being followed and that all surveys are being completed according to the protocol. Study coordinators review participant-level data for missingness. Participants are provided with monetary compensation for every completed assessment period and may receive up to $225 for participating ($75 each for completing the baseline surveys, post-treatment, and 6-month follow-ups).

Data management {19}

Survey data is being collected from participants online through REDCap. Study staff track assessment completion, monitor for missing data, and follow up with participants when missing data are identified. REDCap alerts, reports, and queries are used to minimize missing data and ensure accuracy. Additionally, study staff monitor for data irregularities such as skip patterns and out of range data and completion times. Data are maintained on a secure server accessible only to study staff. The REDCap database requires online sign-in with a username and password assigned to individual study staff. The data system includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Confidentiality {27}

Data are maintained on a Seattle Children's network server with password protection and daily backup of data. The primary source of data comes from online assessments conducted on the REDCap platform hosted at Seattle Children's. REDCap has extensive security precautions appropriate for the storage of Protected Health Information (PHI). REDCap was developed specifically around HIPAA security guidelines and is recommended for use by researchers. 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. Access to servers is restricted to authorized Seattle Children's support personnel. All identifying information is removed from all electronic data, thus protecting the identities of participants.

All study participants are assigned a unique Study ID (e.g., "IMP001") which is connected to their survey data stored on REDCap, along with an email address and/or phone number used to distribute the survey invitations in REDCap. All identifiers stored in REDCap are marked as such using the corresponding fields, which mobilize REDCap's built-in protections for any identifying information. Only study team members have access to the identifiable survey data and other identifying information on REDCap.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A; we are not collecting any biological specimens for this study.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

General analytic procedures

All main analyses are intention-to-treat analyses, including all participants randomized regardless of intervention compliance. Missing values due to dropouts will be imputed with well-established methods that reduce bias in estimates such as multiple imputation, full information maximum likelihood, and empirical Bayes estimation, or multiple imputations with chained equations (MICE), if a substantial amount of missing data exists.

Analyses by aims

Aim 1. Determine the effectiveness of the *Pancreatitis Pain Course* in improving patient-related outcomes. H1: Patients exposed to the *Pancreatitis Pain Course* will have significantly lower pain interference and pain severity immediately after the intervention (two months) and at six-month follow-up compared to the patients exposed to Education control. H2: Patients exposed to the *Pancreatitis Pain Course* will have lower opioid use, depression, anxiety, pain catastrophizing, and stronger improvements in physical functioning, sleep, HRQL, and patient global impression of change compared to patients exposed to Education control.

We will first conduct cross-sectional analysis on all outcomes at the two-month follow-up and six-month follow-up separately, to assess the immediate and long-term effects of the intervention. Given the pragmatic randomized clinical trial design we anticipate most baseline covariates will be balanced across study arms; therefore, only stratification factors (site, diagnosis) will be controlled in the regression models. Our analytic framework is similar for all the primary and secondary outcomes because most of them are continuous variables and assessed at the same time. A detailed model specification is as follows,

$$Y_i = \beta_0 + \beta_1 \times Group_i + \boldsymbol{\beta_3} \times \boldsymbol{x_i} + \epsilon_i,$$

where Y_i is the outcome, i.e., pain interference, at two-month assessment for patient i, $Group_i$ is a binary indicator for treatment group assignment (0=education control, 1=pain self-management), $\boldsymbol{x_i}$ is a vector of baseline stratification factors (site and diagnosis), ϵ_i is the error term. The parameter β_1 estimates the mean difference in outcome between treatment arms, and we can assess its significance (Wald t-test).

In addition, we will conduct longitudinal data analysis to examine how within-subject changes differ by treatment arms. This will be achieved by the following regression model specification:

$$Y_{ij} = \beta_0 + \beta_1 \times Group_i + \beta_2 \times T_j + \boldsymbol{\beta_3} \times Group_i \times T_j + \boldsymbol{\beta_4} \times \boldsymbol{x_i} + b_i + \epsilon_{ij}$$

where Y_{ij} ($j = 1, 2, 3$ for time point baseline, 2- and 6-month) denotes the outcome. For example, the pain interference score for patient i at time point T_j; $Group_i$ is a binary indicator of treatment group assignment ($Group_i = 0$ for Education control, $Group_i = 1$ for CBT intervention); T_j is an indicator of the time point, $Group_i \times T_j$ is the time-by-group interaction, $\boldsymbol{x_i}$ is the baseline stratification factors (site and diagnosis) that need to be controlled for in the regression; b_i is the subject-specific random effect that accounts for the within-subject correlation due to repeated assessments; and ϵ_{ij} is the error term. Adjustments for additional site- and patient-level confounding variables (e.g., concomitant therapy) can also be incorporated into the model. With this model specification, we can examine whether treatment effect varies across time by testing the effect $\boldsymbol{\beta_3}$ in the above regression model. We will estimate the fixed effects using the restricted maximum likelihood method (REML) and test their significance with the Kenward–Roger's approximation of the degrees of freedom.[31] All analyses will be performed using R statistical software.[32]

Additional exploratory analysis examining effect modifications will be conducted by including appropriate interaction terms into above regression models. An exploratory subgroup analysis of the effect of treatment engagement on outcomes will be conducted, where engagement is defined as the number of completed intervention modules. We will use linear mixed effects (LME) regression models consisting of treatment engagement, time, and slopes of improvement (treatment engagement x time). To display significant treatment engagement-by-time interaction effects graphically, we will calculate parameter estimates at high (+1 SD above the mean) and low (-1 SD below the mean) values of treatment engagement.[33] This technique uses all the data in the LME model to calculate model-predicted parameters for different levels of engagement, which clarifies the trajectory of pain interference and pain severity for individuals with high and low engagement.

Aim 3 Exploratory Moderator Analysis. For Aim 3, analyses will extend the regression models in Aim 1 by adding interaction terms (moderator-by-group interaction in cross-sectional analyses, moderator-by- group-by-time interaction in longitudinal analyses). We will conduct moderation analysis to examine whether there are differential intervention effects across age and sex as well as by social determinants of health (SDOH), racial, and ethnic groups. The effect modifications will be examined by including group-by-moderator interaction terms in regression equation (1). Moderation effects will then be tested by assessing the significance of the proper contrast among corresponding regression coefficients. Overall moderation can be assessed with multivariate Wald-type t-statistic, F-statistic and likelihood ratio test (LRT) comparing models with and without interactions. We will also conduct additional subgroup analysis within groups defined by moderators to examine the differential effect sizes within individual subgroups.

Interim analyses {21b}

There are no planned interim analyses; not applicable.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Aim 2 utilizes qualitative data that will be analyzed using a continuous, iterative process. NVivo software will be used for data management and processing. We will extract contextual factors from our interviews to document what facilitates or acts as a barrier to implementation. The Practical, Robust, Implementation and Sustainability Model (PRISM) guides the project; this is an implementation science framework to understand multi-level contextual factors that interact with an intervention.[34] Our qualitative interviews and data analysis align with three of the contextual PRISM domains (1) Perspectives on the intervention (e.g., history with similar programs); (2) Characteristics of implementers, their settings, and those receiving the intervention (patients) (e.g., delivery staff, organizational decision makers and community levels); and (3) implementation and sustainability infrastructure (e.g., resources, and capacity).

Quantitative data, from (1) logins and (2) completed modules, will be integrated with the qualitative data from transcripts of semi-structured interviews with participants. Triangulating our data sources

will allow us to corroborate evidence, prevent researcher bias in interpretation, and increase the confirmability of our qualitative data.[35,36]

We will use a deductive-inductive qualitative analysis to evaluate implementation. The first round of coding will be guided by the PRISM framework (the deductive component): 1) the organizational and patient perspectives of the intervention, 2) characteristics of the patient recipients, and 3) implementation and sustainability infrastructure, with flexibility to include additional domains derived from transcript review. Within each domain, specific constructs may influence implementation. We will also capture emergent themes in the data (the inductive component), which will allow for discovery of themes not included in a priori PRISM codes. We will follow an iterative process whereby analysis will begin at the time of first interview and will inform the direction and content of future data collection.

Qualitative coding of individual interviews will follow established methods using thematic analysis at the semantic/topical level[37] in order to retain stakeholder descriptions of their experiences with the intervention, facilitators, challenges, and solutions to integration of the intervention into their organizations. To promote rigor and transparency in our qualitative data analysis procedures, we will (1) meet to review codes, organize codes into themes, and obtain consensus, (2) employ an iterative coding process so that all codes and themes are compared across surveys to identify similarities and differences, and (3) maintain a coding dictionary to document operational definitions of codes and coding decisions.[38] We will code the data independently and discuss with other team members until an inter-coder agreement rate of 80% is reached for 15% of the data. To maximize inter-coder reliability, the team will meet regularly during data collection and analysis to review emerging themes, reconcile differences in coding, and determine whether modifications to the interview guide are needed for remaining interviews. Discrepant interpretations of interview data during the coding phase will be resolved by consensus during team meetings. We will keep a decision log to document all coding and analytic decisions

Methods in analysis to handle protocol non-adherence and any statistical methods

to handle missing data {20c}

Missing data handling. Given the pragmatic clinical trial design, we expect most missing data will occur in outcomes and likely due to drop out from the study and loss to follow-up. Amount and pattern of missing data will be examined. We will further minimize bias in parameter estimates by using recommended missing data strategies,[39] including multiple imputation, full information maximum likelihood (in Mplus), and empirical Bayes estimation (in HLM).[40,41] If a substantial amount of missing data exists, in addition to our primary data analysis using all available data, we will conduct additional sensitivity analysis using multiple imputations with changed equations (MICE). Missing values are imputed based on the observed values for a given individual and the relations observed in the data for other participants, assuming the observed variables are included in the imputation model. Multiple imputation procedures are very flexible. Because multiple imputation involves creating multiple predictions for each missing value, the analyses of multiply imputed data consider the uncertainty in the imputations and yield accurate standard errors. The MICE approach is a flexible yet powerful technique to address missing data issues and has demonstrated excellent performance in practice.[42,43]

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The study protocol, participant-level data and statistical code used to support the protocol will be provided on request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Seattle Children's Research Institute is primarily responsible for the coordination and oversight of the trial. The two principal investigators (TP and DC) are responsible for the overall conduct of the trial. Seattle Children's Research Institute provides remote monitoring for this study and is responsible for setup of the REDCap data collection platform.

Composition of the data monitoring committee, its role and reporting structure {21a}

N/A: A data monitoring committee is not needed, as the study sponsor deemed the study as low risk and requiring only a local Safety Monitoring Committee, which we describe below in Sect. 22.

Adverse event reporting and harms {22}

This study has been designated as minimal risk by the Seattle Children's Institutional Review Board. Monitoring study safety will occur from the initial screening, throughout the informed consent process, and through study completion under the principal investigators' (TP and DC) supervision. The Data Safety Monitoring Committee (DSMC) is comprised of 4 members external to the study team and they meet twice a year to review study progress and recommend appropriate action regarding adverse events or other safety issues.

In the case of an adverse event believed to be related to the study, documentation is collected to describe the nature of the event and any associated risks. All adverse events are discussed at weekly study meetings, and event reports are provided to the DSMC for quarterly review. The PIs comply with all requirements of the IRB for the reporting of safety data and adverse/serious adverse events. All serious and/or unexpected problems presumed to be related to the study are reported by the PIs to the IRB, the DSMC, and the funding organization within 5 days after discovery. The PIs retain the authority to stop or modify the trial at any time. All actions taken are documented on a case report form.

Frequency and plans for auditing trial conduct {23}

Data quality is verified annually by ensuring investigator compliance with all human subjects and HIPAA requirements. Seattle Children's Hospital's Office of Research Compliance regularly audits all research studies. Automated rules and logic in the study tracking database will safeguard compliance with IRB requirements, informed consent requirements, and adherence to study protocols.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Protocol modifications will be updated on ClinicalTrials.gov and in the participants' consent forms if

participant activities are affected. Study modifications will be communicated to the study team (including co-investigators) and IRB for approval prior to implementation.

Dissemination plans {31a}

Results will be disseminated via publication in peer-reviewed journals, reporting on ClinicalTrials.gov within 12 months of study completion, and presentations to key stakeholders and at professional society meetings. No identifying images or other personal or clinical details of participants will be included in reports of the trial results. A summary of the study findings will be shared with all study participants via email after the final trial endpoint completion.

Discussion

The IMPACT-2 study addresses a critical need for effective, accessible pain management interventions for individuals with painful RAP and CP. This hybrid effectiveness-implementation trial tests the effectiveness of digital CBT vs digital Education and gathers information on challenges and facilitators to implementation in a single trial, accelerating the timeframe for implementing a potentially effective intervention. By leveraging digital technology, this study has the potential to significantly improve access, pain outcomes and quality of life for this population.

There are potential challenges to consider in the conduct of this trial. Recruiting a representative patient population is a challenge that we are addressing through implementing both clinic and community-based recruitment and offering participation without any in person visits, reducing barriers to research participation. We address the challenge of digital access by providing a study iPad and internet hotspot so that we do not exclude individuals who do not have access to compatible devices or reliable internet connections. Finally, considerations around the implementation and sustainability of the *Pancreatitis Pain Course* will be obtained through our qualitative interviews, which will be critical should the intervention demonstrate effectiveness and scalability.

The IMPACT-2 study has the potential to make a significant contribution to pancreatitis pain management in a manner that is safe, accessible, and at low cost. If successful, it could provide a model for integrating digital CBT into routine care, ultimately improving outcomes for this population.

Trial status

The current approved protocol is version 1.0 date 11/5/2024. Recruitment started on May 22, 2024, and is estimated to be complete by March 2027.

Abbreviations

AP: Acute Pancreatitis

BPI: Brief Pain Inventory Short Form

CBT: Cognitive Behavioral Therapy/CBT condition

CFIR: Consolidated Framework for Implementation Research

COEs: Centers of Excellence

COMPAT: Comprehensive Pain Assessment Tool for Chronic Pancreatitis

CP: Chronic Pancreatitis

CPDPC: Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

EDU: Education control condition

GAD-7: Generalized Anxiety Disorder scale

GI: gastroenterology

HIPAA: Health Insurance Portability and Accountability Act of 1996,

HRQOL: Health-related quality of life

IRB: Institutional Review Board

LME: linear mixed effects

LRT: likelihood ratio test

MICE: multiple imputations with changed equations

NIH: National Institutes of Health

HEAL: Helping to End Addiction Long-term

NPF: National Pancreas Foundation

PANQOLI: Pancreatitis Quality of Life Instrument

PCS: Pain Catastrophizing Scale – Short form

PHI: Protected health information

PHQ-9: Patient Health Questionnaire-9

PRISM: Practical, Robust Implementation and sustainability Model (PRISM)

PROCEED: Prospective Evaluation of Chronic Pancreatitis Study

PROMIS: Patient-Reported Outcomes Measurement Information System

RAP: Recurrent Acute Pancreatitis

REDCap: Research Electronic Data Capture

REML: restricted maximum likelihood method

SCH: Seattle Children's

SD: Standard Deviation

SDOH: Social determinants of Health

SCRI: Seattle Children's Research Institute

SMC: Safety Monitoring Committee

TAPS: Tobacco, Alcohol, Prescription Medication Screener

TEI: Treatment Evaluation Inventory

Declarations

Ethics approval and consent to participate {24}

The Institutional Review Board of Seattle Children's Hospital approved the research protocol (STUDY00004693). Written informed consent to participate is obtained from all study participants.

Consent for publication {32}

N/A; we will not present any identifying images or personal/clinical details of participants in reported trial results. Copies of blank consent forms can be provided upon request.

Availability of data and materials {29}

De-identified datasets and data dictionaries will be shared with an NIH-approved repository and will be available for public use with appropriate permissions.

Competing interests {28}

All authors declare no other competing interests.

Funding {4}

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Authors' contributions {31b}

TMP and DC devised the study objectives and design. TMP led the writing of this manuscript. DY, AD, BD, and CZ contributed to the conception of the study and the development of the proposal. BD and TMP contributed to intervention content. OO is the clinical research coordinator, assisting with protocol implementation, participant recruitment, data collection, and participant tracking to ensure adherence to study and intervention protocol. MB, WF, EF, CF, PH, WP, SP, GT, DY, and DC are assisting with the acquisition of study participants. All authors have provided edits, reviewed, and approved the final manuscript.

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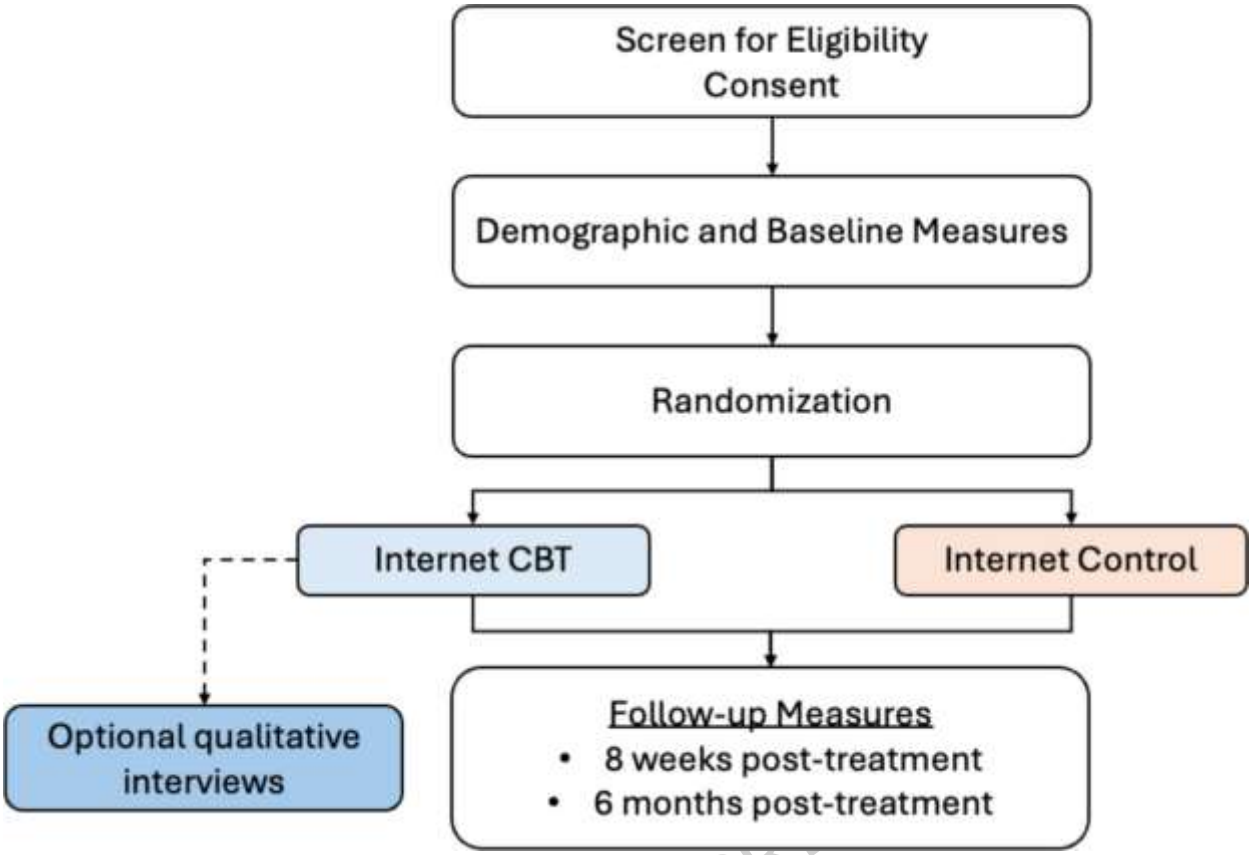

Fig. 1 The study recruitment flow and condition allocation for IMPACT-2

	Enrollment	STUDY PERIOD				
		Pre-Tx Assessment	Allocation	Post-Allocation		Close-Out
TIMEPOINT	$-t_1$	t_1	*0*	*Intervention*	t_2	t_3
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization			X			
INTERVENTION/ COMPARATOR:						
EDU				X		X
CBT				X		
ASSESSMENTS*:						
Demographics and Social Determinants of Health		X				
Medical History		X			X	X
Concomitant Therapies					X	
Substance Use Screener		X				X
PRIMARY OUTCOMES: Pain severity, pain interference		X			X	X
SECONDARY OUTCOMES: disease-specific pain, physical functioning, psychological functioning, pain catastrophizing, sleep disturbance, disease specific health-related quality of life, patient global impression of change, opioid use, treatment acceptability*		X			X	X

Fig. 2 Schedule of enrollment, interventions, and assessments