Tailored Non-Pharmacotherapy Services for Chronic Pain: Testing Scalable and Pragmatic Approaches (RESOLVE Study)

UH3 STUDY PROTOCOL

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Grantee Institution:
Kaiser Permanente Washington Health Research Institute (KPWHRI)

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the following:

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

SUMMARY OF CHANGES

Date	Description of Change (Include specific sections affected)	Rationale for Change
07/15/20	Corrected the description of clinical trial phase to phase III; it was incorrectly stated as phase IV. 1.1 Synopsis 4.1 Overall Design	Inaccuracy in text
07/15/20	Added description of subgroup analyses based on age and race/ethnicity, as required for NIH phase III clinical trial. 3.4 Exploratory (Tertiary) Objectives 15.7 Additional Effectiveness Analyses for Primary Outcome (Moderators and Mediators)	Required by NIH and requested by NIA
08/06/20	Corrected description of modified BPI-SF to be 11 items (vs. 10 items) and pain intensity subscale to be 4 items (vs. 3 items) 3.1 Primary Objective 3.2 Secondary Objectives	Inaccuracy in text
08/06/20	Added final info on perceived support measure to mediator table 3.4 Exploratory (Tertiary) Objectives	Finalized based on pilot study completion
08/06/20	Changed randomization stratification based on sex to be based on EHR data and not self-reported sex in baseline survey 4.3 Study Arm Assignment/Randomization	Changed due to ability to ensure availability of EHR variable (i.e., not missing)
08/06/20	Added information on KP CHR (KPNW) as site of virtual health coaches 10.1 Description of Interventions	Update to team structure/ intervention staffing
09/25/20	Changed KPGA site PI from Dr. Bradlyn to Dr. McCracken since Dr. Bradlyn is retiring and revised page to just include contact info and not signatures Page iii. Investigator Contact Information	Current KPGA site PI is retiring in Dec. 2020
09/25/20	Edited the follow-up data collection windows to reflect final data collection decisions: 3-month changed to 80-140 days (from 75-110); 6-month changed to 170-230 days (from 165-200); and 12-month changed to 350-410 days (from 345-480). In addition, revised description of duration of active intervention to clearly specify max. duration is 12 weeks by moving to footnote in Table 1. 1.2 Schedule of Activities and Table 1	Changed to reflect final decisions related to follow-up data collection
09/25/20	Added assessment of MCID for two subscales of pain severity composite measure (MCID in pain intensity and MCID in pain-related interference) 3.2 Secondary Outcomes 15.6 Secondary Effectiveness Analyses	In response to DSMB recommendation
09/25/20	Added rural/medically underserved residency as stratum for randomization and adjustment variable 4.3 Study Arm Assignment/Randomization 15.5 Primary Effectiveness Analyses	In response to DSMB recommendation

Date	Description of Change (Include specific sections affected)	Rationale for Change
09/25/20	Specified one additional EHR-based inclusion criterion to be applied at KPWA site only: no opioid use disorder (OUD) ICD-10 codes 5.1 Participant Inclusion Criteria	To ensure coordination with another HEAL study at KPWA site specifically treating those with pain and OUD
09/28/20	Added step to recruitment process where patients who are referred by their clinician can contact the study staff directly. For these individuals, consent to access their medical record to assess eligibility will be obtained. 6.1 Recruitment of Patients 8.1 Informed Consent of Patients	Another method was identified by health care system stakeholders and accommodated by study for how patients might be referred
09/28/20	Added ClinicalTrials.gov registration info to the title page	Study registration with ClinicalTrials.gov was posted 08/24/20
11/10/20	Removed statement related to obtaining waiver of written consent and alteration of HIPAA from IRB as it was not accurate. 8.1 Informed Consent of Patients	Removed at request of VUMC IRB
11/10/20	Revised the section on informed consent to clearly delineate consent processes related to screening and study enrollment.	Revised in response to VUMC IRB questions
11/23/20	Clarified that no consent is required for the population EHR-based eligibility screening 8.1 Informed Consent of Patients	Revised at request of VUMC IRB
11/23/20	Clarified that sample of patients who do not complete the active interventions and will participate in qualitative interviews are still enrolled in the study. This is already specified in section 9.1, which has not been edited, but text was added to other places in protocol where these interviews are described. 3.5 Qualitative Evaluation Objectives 6.1 Recruitment of Patients 11.3 Qualitative Interviews	Add text to clarify in response to VUMC IRB questions
11/24/20	Added text to indicate virtual intervention sessions completed by secure video encounter that are recorded will generate a video recording 2.4.1 Potential Risks 17 Source Documents	Finalization of procedures related to recording virtual sessions
11/24/20	Added Ms. Firemark as staff person involved in intervention supervision and fidelity monitoring 10.4 Study Intervention Fidelity Monitoring Procedures	Finalization of staff/study team roles
03/22/21	Updated info on number of health coach interviews from “up to 10” to reflect that all coaches (currently projected at 12 so described as “approx.12”) will be offered to complete an interview 1.1 Synopsis 6.2 Recruitment of Stakeholders for Qualitative Evaluation 11.3 Qualitative Interviews	Finalization of hiring/staffing of health coaches

Date	Description of Change (Include specific sections affected)	Rationale for Change
03/31/21	Modified EHR-based inclusion criteria related to the minimum number of pain-related encounters (criterion #4 in section 5.1) for the 3 KP sites; changed to ≥ 2 encounters that are at least 30 days apart. Essentia remains at least 1 encounter. 5.1 Participant Inclusion Criteria	High rate of refusal prior to screening due to no chronic pain and ineligibility among those screened at KP sites. By increasing threshold for required pain visits, more likely to efficiently identify people likely to have chronic pain.
03/31/21	Added an EHR-based exclusion criterion related to surgery in the past 60 days for all sites 5.2 Participant Exclusion Criteria	High rate of refusal and reporting recent surgery and therefore no current chronic pain. By adding criterion, more likely to efficiently identify people likely to have chronic pain.
03/31/21	Added exclusion criterion related to planned/scheduled surgery in next year. 5.2 Participant Exclusion Criteria 7 Eligibility Screening	Multiple virtual health coach intervention participants have indicated upcoming surgery; common exclusion criterion for pain studies
03/31/21	Updated description of virtual intervention fidelity monitoring to include more details and specific info on final plan. 10.4 Study Intervention Fidelity Monitoring Procedures	Provide more details on final plan/procedure
03/31/21	Added information on third framework to be used in qualitative evaluation, Theoretical Framework of Acceptability 16 Qualitative Evaluation Analyses	Expanded constructs for qualitative interviews to include more related to acceptability
02/24/22	Revised description of active interventions throughout entire document to clarify painTRAINER as “CBT-based.” This affected wording in many places throughout protocol. Most significantly, it changed Aim #1 wording from this: **Aim #1:** Determine the effectiveness of a web-based CBT-CP program and virtual coach-led (telephonic/video) CBT-CP on achieving clinically meaningful improvements in patients’ pain severity (pain intensity + pain-related interference) relative to those receiving usual care at 3 months. To revised: **Aim #1:** Determine the effectiveness of an online, CBT-based pain management program and virtual coach-led (telephonic/video) CBT-CP on achieving clinically meaningful improvements in patients’ pain severity (pain intensity + pain-related interference) relative to those receiving usual care at 3 months.	NIH Project Scientist, Dr. Wandner, requested edit; using the consistent description of painTRAINER as CBT-based and not CBT was agreed upon for all HEAL studies that include painTRAINER.

Date	Description of Change (Include specific sections affected)	Rationale for Change
02/24/22	Removed references to painTRAINER as an "application" and replaced with "online program" as it is not an application ("App") that can be downloaded to a mobile device but can only be used online via a web browser. Also removed "web-based" as descriptor and replaced with "online" as it is clearer to describe as "online CBT-based." (vs. web-based, CBT-based)	"Application" was inaccurate description.
02/24/22	Revised description of active interventions throughout entire document to be independent/standalone. Previously, painTRAINER had substantial detail but the virtual coach-led CBT-CP was only described as "having content analogous to painTRAINER." The structure of Section 10 was changed to provide an overview of the core elements of both interventions and then give specifics on each one. Precis Section 10 Study Interventions	Both active interventions needed equal description and previous text inaccurately presented the coach-led intervention as derived from painTRAINER.
02/24/22	Added descriptions of the onboarding and ongoing support/outreach for both active interventions. In addition, described the motivational interviewing language included in the painTRAINER onboarding script. Section 10 Study Interventions	Requested by DSMB
02/24/22	Added this information in each location where 2,380 enrollment target is stated: Note: The number enrolled might need to be greater than 2,380 to ensure reaching the randomized participant target of 2,331 (as not all who consent/enroll go on to be randomized).	Clarify that the target number consented/enrolled is variable and may change in order to meet the 2,331 target for number randomized, which is invariable.
02/24/22	Clarified that intervention staff who support participant engagement with painTRAINER will also be invited to complete qualitative interviews. 1.1 Synopsis 6.2 Recruitment of Stakeholders for Qualitative Evaluation 11.3 Qualitative Interviews	Oversight in original description as just stated "health coaches"
02/24/22	Added information to Section 8.1 indicating that, as needed, sites may follow-up by phone with individuals who enrolled by web in order to briefly welcome them to the study and clarify next steps. Section 8.1 Informed Consent	Added as a contact and strategy to support retention.
11/10/22	Updated Dr. DeBar's KP site affiliation to KP CHR (as of 1/1/23). Removed Dr. Elder as KP CHR site PI. Added Dr. Cook as KPWHRI site PI. Section: Investigator Contact Information	Dr. DeBar is transferring to KP CHR (as of Jan. 1, 2023) and it will become the prime site.

Date	Description of Change (Include specific sections affected)	Rationale for Change
11/10/22	Updated the number to be enrolled to approximately 2,500 from 2,380. Clarified that the total number enrolled and randomized by each of the 4 sites may vary (range of 595-625) in order to reach the overall study target for number randomized within the study timeline with some sites enrolling more than others (i.e., Essentia and KPGA vs. KPWA). 1.1 Synopsis 6.1 Recruitment of Patients	As the study nears the end of recruitment, we are aiming to enroll more at Essentia and KPGA where enrollment rates have remained steady in order to ensure we have the overall target N. KPWA rates have been lower than the other sites and seem to be decreasing slightly in recent months. This approach was approved by NIA and JHU via email on 10/31/22.
11/10/22	Clarified the target N to be randomized is at least 2,331 or 777 per arm. 1.1 Synopsis 6.1 Recruitment of Patients 15.1 Sample Size Determination	Clarify that the N randomized will not be exactly 2,331 but might be slightly over.
11/10/22	Indicated that up to 2 interviews will be conducted with each healthcare system stakeholder and that interviews will be conducted in years 4-5 of the study (vs. years 2-3). 1.2 Schedule of Activities 3.5 Qualitative Evaluation Objectives	Study team would like to be able to interview healthcare system stakeholders more than one time.

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LIST OF ABBREVIATIONS

AE	Adverse Event
BPI - SF	Brief Pain Inventory – Short Form
CBT-CP	Cognitive Behavioral Therapy for Chronic Pain
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CI	Confidence Interval
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CSI	Clinical Site Investigator
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDA	Exploratory Data Analysis
EDC	Electronic Data Capture
EH	Essentia Health
EHR	Electronic Health Records
EQ-5D-5L	EuroQoL 5 Dimensions – 5 Levels
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HCS	Health care system
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
JHU	Johns Hopkins University
KP	Kaiser Permanente
KP CHR	Kaiser Permanente Center for Health Research
KPGA	Kaiser Permanente Georgia
KPNW	Kaiser Permanente Northwest
KPWA	Kaiser Permanente Washington
KPWHRI	Kaiser Permanente Washington Health Research Institute
MCID	Minimal Clinically Important Difference

mHealth	Mobile Health
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIA	National Institute on Aging
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OR	Odds Ratio
PEG	Pain, Engagement of Life & General Activity
PCP	Primary Care Providers
PHI	Protected Health Information
PI	Principal Investigator
PO	Program Official, NIH
PROMIS	Patient-Reported Outcomes Measurement Information System
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QC	Quality Control
QoL	Quality of Life
RIC	Recruitment Innovation Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIRB	Single Institutional Review Board
SOP	Standard Operating Procedure
TIC	Trial Innovation Center
UC	Usual Care Study Arm / Group
UP	Unanticipated Problem

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	*Tailored Non-Pharmacotherapy Services for Chronic Pain: Testing Scalable and Pragmatic Approaches (RESOLVE Study)*
Précis:	The RESOLVE study is a multicenter comparative effectiveness trial evaluating two cognitive-behavioral therapy (CBT)-based chronic pain treatments delivered via different telehealth modalities: 1) online program and 2) live, coach-led, virtual sessions (telephone and/or video conference). The study uses a 3-arm, parallel intervention design; both intervention arms will be compared to usual care services. Participants randomized to the two intervention arms will complete 8 CBT-based sessions for chronic pain (approximately 1 per week) via the online program (self-directed) or one-on-one with the live coach. Those randomized to usual care will receive an education resource manual for chronic pain management. All study participants will be enrolled for 12 months and complete self-reported assessments at baseline, notification of randomization, and 3-, 6- and 12-months. A subset of participants will participate in the qualitative evaluation and complete an hour-long interview at approximately 3-5 months follow-up and 12-14 months follow-up. In addition, qualitative interviews will be completed with approximately 20 health care system stakeholders across the 4 study sites and the staff who support the painTRAINER intervention administration and those who deliver the virtual CBT-CP sessions (approximately 12).
Specific Aims:	**Aim #1:** Determine the effectiveness of an online, CBT-based pain management program and virtual coach-led (telephonic/video) CBT-CP on achieving clinically meaningful improvements in patients' pain severity (pain intensity + pain-related interference) relative to those receiving usual care at 3 months. **1a.** Examine the impact of the active interventions on secondary pain outcomes and related quality of life outcomes (social role functioning, physical functioning, and patient global impression of change); as well as exploratory outcomes, which include long-term opioid use; comorbid symptomology (depression, anxiety, and sleep disturbance); and high impact chronic pain and graded chronic pain. **1b.** Conduct subgroup analyses to determine the impact of the active interventions on specific populations and explore for potential heterogeneity of treatment effects by sex; rural/medically underserved residency; multiple pain conditions; mental health mood disorders; and negative social determinants of health. **1c.** Examine the role of theory-based mediators, pain catastrophizing, pain-related self-efficacy, and perceived support, on pain-severity. **Aim #2:** Assess the cost and incremental cost-effectiveness of the online and virtual coach-led CBT-CP interventions compared to each other and usual care. **Aim #3:** Conduct a qualitative evaluation to understand: 1) patient experiences of the interventions, including how they relate to treatment

	response, variability by site, and rural/medically underserved residency status; and 2) health system issues, including adaptations and contextual factors at the site and external levels, barriers and facilitators to intervention success and potential for adoption, sustainability, and dissemination.
Population:	Approximately 2,500 participants with high-impact chronic pain, as demonstrated by initial electronic health records (EHR)-based eligibility criteria and subsequent screening, will be enrolled in this study with the goal of randomizing approximately 2,331 participants (at least 777 per study arm). [Note: The number enrolled might need to be greater than 2,500 to ensure reaching the randomized participant target of at least 2,331 (as not all who consent/enroll go on to be randomized).] Participants will be recruited from four integrated health care systems/clinical sites: 1) Kaiser Permanente Georgia (KPGA), 2) Kaiser Permanente Northwest (KPNW), 3) Kaiser Permanente Washington (KPWA), and 4) Essentia Health. Of the randomized participants, 120 will participate in the interviews for the qualitative evaluation. The health care system stakeholders to be interviewed will be administrators in the areas of quality improvement, primary care, and/or pain management at each of the 4 study sites and referring clinicians. The intervention / health coaching staff to be interviewed will be the centralized staff who support painTRAINER engagement as well as those who deliver the virtual CBT-CP sessions.
Phase:	Phase III Clinical Trial
Anticipated Number of Sites:	Four clinical sites: 1. Kaiser Permanente Georgia (KPGA) 2. Kaiser Permanente Northwest (KPNW) 3. Kaiser Permanente Washington (KPWA) 4. Essentia Health
Description of Interventions:	Two interventions will be tested in this comparative effectiveness trial. 1) An online, CBT-based pain coping skills training program (painTRAINER) 2) A virtual, live coach-led CBT-CP intervention (telephone or video-administered) Both interventions are comprised of 8 sessions which participants are expected to complete weekly. The content of the 2 interventions is analogous and focuses on interactive training in evidence-based pain-coping skills. Those randomized to the usual care arm of the study will be sent a bound copy of the 2020 edition of the *American Chronic Pain Association Resource Guide to Chronic Pain Management*. All enrollees can receive any pharmacologic and nonpharmacologic treatments available to them without restriction.
Study Duration:	48 months from start of enrollment to completion of data analyses

Subject Participation Duration:	12-14 months (The majority of subjects will participate for 12 months. The subset of qualitative evaluation subjects will complete the last follow-up interviews at 12-14 months.)
Estimated Time to Complete Enrollment:	25 months

1.2 Schedule of Activities (SoA)

The schedule of activities in **Table 1** below pertains to the patients who will participate in the RESOLVE UH3 trial.

For the health care system stakeholders who participate, study activities will include approximately two hour-long interviews conducted by phone. For the health coach / intervention staff who participate, study activities will include two approximately hour-long interviews conducted by phone early and later in the study implementation.

Table 1. UH3 Schedule of Activities for Patients

Procedures	Eligibility Screening and Consent[1] Day -14 to -1 or Day 0	Baseline and Randomization[1] Day 0	Randomization Notification Approx. Day 1 to 7	Intervention Session #1 Approx. Day 8 to 14	Intervention Session #2 Approx. Day 15 to 21	Intervention Session #3 Approx. Day 22 to 28	Intervention Session #4 Approx. Day 29 to 35	Intervention Session #5 Approx. Day 36 to 42	Intervention Session #6 Approx. Day 43 to 49	Intervention Session #7 Approx. Day 50 to 56	Intervention Session #8[2] Approx. Day 57 to 63	3-Month Follow-Up Day 80 to 140	6-Month Follow-Up Day 170 to 230	12-Month Follow-Up / Final Assessment Day 350 to 410
Eligibility screening	X (or) X													
Informed consent	X (or) X													
Baseline assessment		X												
Randomization		X												
Notification of study arm assignment			X											
Administer study intervention (if applicable, based on study arm assignment)				X	X	X	X	X	X	X	X			
Adverse event review and evaluation			X----------											----------X
Study assessments completion		X	X									X	X	X
Interviews with subset of participants												X		X

1. The eligibility screening, consent and baseline survey can all be completed in the same phone encounter or online survey session, if feasible for the participant. If these activities are not completed in the same encounter or session, efforts will be made to complete the consent and baseline survey with those eligible individuals who want to participate in the study within 14 days of them completing the eligibility screening.
2. The active intervention sessions are intended to occur approximately weekly over the course of 8 weeks; however, completion may vary due to personal circumstances of the participants. The maximum duration for active intervention sessions is 12 weeks. (See Section 10.2 for further information).

2 INTRODUCTION

2.1 Background Information

Chronic pain, defined as pain lasting for 3 months or longer, is one of the most common, disabling, and costly public health problems in the United States.[1] It is one of the primary reasons patients seek medical care. It often involves high levels of disability and emotional suffering.[1,2] High impact chronic pain, defined as pain that has lasted 3 months or longer and is accompanied by at least one major activity restriction, such as being unable to work outside the home, go to school, or do household chores affects about one in ten adults.[1,3,4]

Rural residency is associated with higher prevalence of high impact chronic pain with complicating features such as depression and medical comorbidities.[5,6] Rural residents with chronic pain report higher pain frequency and intensity and more pain-related disability and depression than urban residents with pain.[7,8] Health care disparities between rural and urban areas are widely recognized with rural residents often affected by difficulties in availability, accessibility, and affordability of health services.[9] These disparities put rural patients with chronic pain at higher risk for adverse outcomes and suboptimal pain management.

Most patients with chronic pain are treated by primary care clinicians and medications are mainstays of pain management. While opioids were, until recently, viewed favorably for long-term chronic pain management, supporting evidence was weak.[10] Recent evidence shows opioid-related harms and widespread opioid use has left an aftermath of adverse effects for patients and communities.[11,12] These consequences have been especially pronounced in rural communities where the abuse rates of prescription opioids and drug-related overdoses are disproportionally higher than in urban areas.[13,14] Consequently, primary care clinicians and their patients, especially in medically underserved areas, urgently need increased access to viable nonopioid options and treatments for long-term chronic pain management.

Cognitive-behavioral therapy for chronic pain (CBT-CP) is the most widely accepted and effective treatment[1,15,16] and is shown to benefit low-literacy adults in rural areas.[17] CBT-CP is based on the theory that patients' beliefs, attitudes, behavior, and coping styles play central roles in determining (mediating) the impact of persistent pain.[18] CBT-CP effects can be maintained long after treatment ends, without the negative side effects of opioids and other pain medications. CBT-CP is an attractive adjunct or alternative to pharmacological treatments. It focuses on helping patients develop and master skills to manage pain and its associated disability and emotional distress to improve functioning and quality of life. The National Pain Strategy calls for wider implementation of CBT-CP self-management programs,[19] noting that despite supporting evidence, [20-29] CBT-CP implementation lags due to significant barriers.

Outside Veterans Affairs health care systems,[20] few clinicians are trained to deliver CBT-CP. CBT-CP services in community practice often vary in quality despite the growing emphasis on standardized training methods.[21] In community settings, fidelity to best treatment practices is rarely assessed.[22] Frontline behavioral health providers offering CBT-CP generally have high caseloads and pressure to prioritize treatment for mental disorders, limiting CBT-CP availability. These problems are especially critical in rural areas and medically underserved communities[7,9,23] where there are generally few behavioral health and psychotherapy providers and extreme scarcity in those trained to deliver CBT-CP.[24] In addition, conventional CBT-CP programs can be difficult to use for patients with limited time, transportation or mobility barriers,

or competing demands. Most CBT-CP programs require weekly in-person sessions of 50 minutes or more over 2-3 months, often in group formats with inflexible scheduling. Patients referred for CBT-CP may attend too few sessions to receive an adequate treatment dose.[25] Further, the stigma associated with what are perceived to be "psychological" interventions can limit patient uptake.[26,27] Providing CBT-CP by telephone or in an online program may help destigmatize its use and encourage patients to view it as complementing conventional medical management of chronic pain, while helping them achieve functional and quality-of-life goals.

Lastly, there are gaps in primary care providers' (PCP) referral to CBT treatment. PCPs who lack familiarity with CBT-CP are often concerned about not having enough time to discuss CBT-CP, lack ways to provide a compelling rationale for CBT-CP, or have difficulty explaining why a psychologically informed treatment may help manage a physical condition. Moreover, guidelines do not exist for determining which patients might benefit from CBT-CP.[2]

Technologies to deliver and assist treatment such as online- and telephone-based treatment programs[28-30] offer ways to increase access to evidence-based pain care, including CBT-CP and related self-management approaches.[31,32] Because mobile health (mHealth) and telehealth services have lower marginal costs than in-person care, they can reach large numbers of patients and support health behavior change and self-management efforts while overcoming system, patient, and clinician barriers.[33] mHealth interventions can improve self-management[33] and chronic illness care outcomes.[34] Finally, following the Covid-19 outbreak, mHealth and telehealth services are rapidly becoming the norm with a particular push towards video visits both to best approximate in-person visits and increase likely payment.[35] Further, as Eccleston and colleagues (2020) note, "preventing [and managing] chronic pain is complex at the best of times but in a global health pandemic, risk factors for pain morbidity and mortality will be magnified. (p.8904)"[36]

2.2 Rationale

High impact chronic pain is persistent and limits life and work activities. It affects about one in ten adults.[1,3] Treatment is inadequate, with overuse of long-term opioid therapy and underuse of evidence-based nonpharmacologic treatments.[15] Cognitive-behavioral therapy for chronic pain (CBT-CP) is the most widely accepted and effective of these treatments.[1,15,16] Enhanced availability of CBT-CP services for high impact chronic pain is of critical public health importance[37], particularly for medically underserved and rural populations devastated by the opioid epidemic.[13,14] However, professionals trained to deliver CBT-CP are typically in urban areas. Making CBT-CP widely available and low cost would reduce barriers to use of CBT-CP for the majority of the US population, particularly those in rural and medically underserved areas.

This comparative effectiveness research trial will evaluate two potentially low-cost and scalable CBT-based treatments for chronic pain: 1) an established online, CBT-based pain coping skills training (PCST) program (painTRAINER), and 2) a virtual, coach-led (telephone/video-administered) CBT-CP intervention. Both modalities will be compared to usual care services.

2.3 Specific Aims

Aim #1: Determine the effectiveness of an online, CBT-based pain management program and virtual coach-led (telephonic/video) CBT-CP on achieving clinically meaningful improvements (≥ 30%) in patients' pain severity (pain intensity + pain-related interference) relative to those receiving usual care at 3 months.

1a. Examine the impact of the active interventions on secondary pain outcomes and related quality of life outcomes (social role functioning, physical functioning, and patient global impression of change); as well as exploratory outcomes, which include long-term opioid use, comorbid symptomology (depression, anxiety, and sleep disturbance), and high impact and graded chronic pain.

1b. Conduct subgroup analyses to determine the impact of the active interventions on specific populations and explore for potential heterogeneity of treatment effects by sex; rural/medically underserved residency; multiple pain conditions; mental health mood disorders; and negative social determinants of health.

1c. Examine the role of theory-based mediators, pain catastrophizing, pain-related self-efficacy, and perceived support, on pain-severity.

Aim #2: Assess the cost and incremental cost-effectiveness of the online and virtual coach-led CBT-CP interventions compared to each other and usual care.

Aim #3: Conduct a qualitative evaluation to understand: 1) patient experiences of the interventions, including how they relate to treatment response, variability by site, and rural/medically underserved residency status; and 2) health system issues, including adaptations and contextual factors at the site and external levels, barriers and facilitators to intervention success and potential for adoption, sustainability, and dissemination.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

The RESOLVE study poses minimal risks. Those risks that might exist fall into four categories: (a) risks of the intervention; (b) risks associated with research assessments; (c) risks associated with potential loss of confidentiality; and (d) risks of worsening physical or emotional state. These minimal risks and the procedures to help mitigate the risks are described further below.

Risks associated with the intervention. The intervention programs consist of either an online program or virtual coach-led (telephone and/or video) CBT-CP sessions. CBT-CP focuses on helping people change how they think and act in response to pain-related stressors[38] and on increasing patients' coping skills to help them better manage their pain and improve their emotional and physical functioning. Therefore, individuals who participate in the interventions might experience emotional or physical discomfort related to challenges in modifying their thoughts and behaviors related to pain. For example, someone might feel discouraged or frustrated during the intervention process or they might be physically challenged by behaviors they try to address in increasing physical activity. However, these risks are minimal, in that the probability and magnitude of

discomfort is no greater than what someone might encounter in daily life. CBT-CP interventions have been used by the current study team and other investigators without adverse effects in studies as well as in clinical practice with patients with chronic pain and other health conditions.
Procedures to help mitigate these risks. All behavioral health staff who will be conducting the intervention sessions with participants will receive comprehensive training and supervision from one or more of the following individuals: Drs. DeBar (PI), Balderson (Co-Investigator at KPNW), and Keefe (Co-Investigator at Duke University), all with considerable experience supervising and training the delivery of such clinical research interventions. Finally, participants who experience emotional or physical discomfort during the intervention have the option of seeking services in the participating health care system in which they are insured/served as well as outside of the health care system, if they prefer; enrollees can receive any pharmacologic or non-pharmacologic treatments available to them without restriction.

Risks associated with research assessments. Research assessments consist of accessing data from participants' electronic health records (EHR) data, conducting surveys and interviews, and collecting data related to the delivery of the intervention programs, including audio- and video-recordings of virtual CBT-CP sessions and the collection of painTRAINER usage data. Any risks related to the collection of research data and the potential for accidental disclosure of protected health information (PHI), are described specifically below. Survey and interview questions focus on pain and associated impairment and functioning, comorbid conditions (including depression and anxiety), and use of treatments outside of traditional health care. Some of the questions might make participants feel uncomfortable. However, the study surveys and interviews involve no specific risk or discomfort beyond those associated with a standard clinical interview. Proposed assessment tools, or ones assessing similar domains, have been used by the research team in previous research, with no known problems or distress on the part of participants. Virtual intervention sessions will be audio- or video-recorded, for the purpose of review by senior research staff, who will make quality assurance ratings of staff performance. (Note: The audio recording of the session is the only data needed for quality assurance review, however if the participant completes a session via video, the recording will generate a video recording from which the audio recording will be extracted.) If participants are uncomfortable with having their session recorded, they can refuse having their session recorded and still participate in the study.
Protection for risks associated with research assessments. Participants will be told that they are free not to respond to specific survey or interview questions or to terminate involvement in completing a survey or interview at any time, with no adverse consequences. If a participant appears to be distressed during assessments, research staff will halt the survey or interview and offer to call back to complete the assessment. The assessment will only re-commence when and if the participant reports feeling capable of doing so. Survey assessments will be conducted by research staff who are trained to address anticipated participant concerns; interviews will be conducted by experienced research staff who have previously conducted interviews with the target population and are sensitive to these issues.

Risks associated with potential loss of confidentiality. The confidentiality of participants could be compromised by an accidental release of protected health information (PHI) that are accessed or collected as part of this study's research assessments. The recruitment design used in this study carries the potential risk of loss of privacy and or

unwanted contacts because EHR data are queried, and pertinent information extracted for potentially eligible individuals. As in any research study, there is the slight risk that records might be accessed or obtained by persons who are not authorized to do so. Procedures to help mitigate these risks. All participant information is considered confidential and will be used only for research purposes. This confidentiality will be ensured through several mechanisms. Each participant will be assigned a study ID and direct identifiers will only be linked to subjects' study ID in circumstances where staff need to access information in order to contact participants to conduct study activities. Analytic datasets will be de-identified. All study forms, paper and electronic records, and all participant data (both hard copies and electronic) will be stored in secure areas, with access restricted to select study staff, or on secure servers, as relevant at the participating institutions. Third, access to participant data and information will be restricted to authorized personnel as necessitated by their professional role and tasks on the project. Data transfer between participating institutions will be done using Secure Socket Layer (SSL) encryption. In accordance with HIPPA regulations and local IRB requirements, all appropriate compliance requirements for data transfer and data use will be met after consultation with compliance officers.

Risks of worsening mental or emotional state. Many of the study participants are expected to have comorbid depression, anxiety and/or other mental health conditions. It is expected that mental and emotional symptoms experienced by these individuals will fluctuate throughout the study period and some participants may have worsening pain and/or other mental health symptoms during the study period. However, these are risks inherent in the population and would occur regardless of study enrollment. Procedures to help mitigate these risks. All patient participants enrolled in the study will have access to treatment through their health care system and will be encouraged to seek care in the event that their symptoms significantly worsen during the intervention. This is consistent with the standard of care provided within the participating health care systems (KPGA, KPNW, KPWA, and Essentia). Participants in the study are free to withdraw from the study at any time with no consequence to their health care. If a patient reports imminent risk of a psychiatric crisis, study staff will take appropriate immediate action by connecting the patient with emergency services in his/her region.

2.4.2 Potential Benefits

Potential benefits for those participating in the intervention arms of the study include access to evidence-based intervention programs that may help participants develop the skills to better manage their pain, improve their functioning, and potentially lower their reliance on opioid medication. While those in the usual care arm will not receive such care, the *American Chronic Pain Association Resource Guide to Chronic Pain Management*[39] is detailed and comprehensive and may help them better navigate the treatment options available to them through their health care system and surrounding communities.

Although patients, clinical staff, and administrators participating in the interview portions of the study may not directly benefit from participation in interviews, many individuals enjoy the opportunity to provide their opinions and tell their stories. Further, these individuals may derive personal satisfaction from being part of a study that may have public health implications and that will further scientific knowledge concerning various treatment and self-care options for pain management.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary Objective

Primary Objective	Brief Description of Measure	Outcome Measured By	Time Frame
Determine whether the active interventions result in a higher proportion of patients achieving a reduction in pain severity that is a minimal clinically important difference (MCID) relative to those receiving usual care at 3 months.	Minimal clinically important difference (MCID) in pain severity (pain intensity + pain interference) is defined as a 30% decrease in score on modified 11-item version of the Brief Pain Inventory – Short Form (BPI-SF)[40-42] from baseline (consistent with IMMPACT consensus guidelines)[43] (Binary; Yes/No)	Patient self-reported pain at baseline and 3 months	Baseline to 3 months

3.2 Secondary Objectives

Secondary Objectives	Brief Description of Measure	Outcome Measured By	Time Frame
Determine whether the active interventions result in a higher proportion of patients achieving a MCID in pain severity relative to those receiving usual care at 6 and 12 months.	See above (Binary; Yes/No)	Patient self-reported pain at baseline, 6 and 12 months	Baseline to 6 and 12 months
Determine whether the active interventions result in a higher proportion of patients achieving a MCID in pain intensity	Minimal clinically important difference (MCID) in pain intensity is defined as a 30% decrease in score on 4-item pain intensity subscale of the Brief Pain Inventory – Short Form (BPI-SF)[40-42] from baseline (Binary; Yes/No)	Patient self-reported pain at baseline, 6 and 12 months	*Primary:* Baseline to 3 months *Secondary:* Baseline to 6 and 12 months
Determine whether the active interventions result in a higher proportion of patients achieving a MCID in pain-related interference	Minimal clinically important difference (MCID) in pain intensity is defined as a 30% decrease in score on 7-item pain-related interference subscale of the Brief Pain Inventory – Short Form (BPI-SF)[40-42] from baseline (Binary; Yes/No)	Patient self-reported pain at baseline, 6 and 12 months	*Primary:* Baseline to 3 months *Secondary:* Baseline to 6 and 12 months

Secondary Objectives	Brief Description of Measure	Outcome Measured By	Time Frame
Examine the impact of the active interventions on pain severity	Brief Pain Inventory – Short Form (BPI-SF)[40-42] (11 items; continuous)	Patient self-reported pain at baseline, 3, 6 and 12 months	*Primary* Baseline to 3 months *Secondary* Baseline to 6 and 12 months
Examine the impact of the active interventions on pain intensity	Pain intensity subscale of the BPI-SF (4 items; continuous)	Patient self-reported pain at baseline, 3, 6 and 12 months	*Primary* Baseline to 3 months *Secondary* Baseline to 6 and 12 months
Examine the impact of the active interventions on pain-related interference	Pain-related interference subscale of the BPI-SF (7 items; continuous)	Patient self-reported pain at baseline, 3, 6 and 12 months	*Primary* Baseline to 3 months *Secondary* Baseline to 6 and 12 months
Examine the impact of the active interventions on social role functioning	PROMIS Ability to Participate in Social Roles 4A[44] (4 items; continuous)	Patient self-reported social role functioning at baseline, 3, 6 and 12 months	*Primary* Baseline to 3 months *Secondary* Baseline to 6 and 12 months
Examine the impact of the active interventions on physical functioning	PROMIS Physical Functioning Short Form 6b (6 items; continuous)	Patient self-reported physical functioning at baseline, 3, 6 and 12 months	*Primary* Baseline to 3 months *Secondary* Baseline to 6 and 12 months
Examine the impact of the active interventions on patient global impression of change (PGIC)	Guy/Farrar Patient Global Impression of Change (1 item each for pain status and overall status)	Patient self-reported impression of change at 3, 6 and 12 months	*Primary* Baseline to 3 months *Secondary* Baseline to 6 and 12 months

3.3 Economic Evaluation Objectives

Economic Evaluation Objectives	Brief Description of Measure	Outcome Measured By	Time Frame
Assess the costs and incremental cost-effectiveness of the active interventions compared to each other and usual care	Costs based on health care utilization and intervention costs will be assessed. Using the framework of cost-effectiveness, the incremental cost per additional patient with a MCID in pain severity (30% reduction from baseline) will be estimated at 12 months, and the quality-adjusted life year (QALY) gained—utilities will be estimated using the EQ-5D-5L.[45]	Health care utilization costs: EHR data costed using standard costing algorithms[46,47] and Medicare fee schedules Intervention costs: Process data related to all relevant resources used in the intervention delivery EQ-5D-5L: Patient self-report at baseline, 3-, 6- and 12-months	Baseline to 12 months

3.4 Exploratory (Tertiary) Objectives

Exploratory Objectives	***Brief Description of Measure***	***Outcome Measured By***	**Time Frame**
Examine the impact of the active interventions on long-term opioid use	Opioid prescription orders or fills indicating a continuous ≥ 60-day supply during the prior 90-day period; account for prescriptions prior to 90-day look-back which carry into the assessment period (Binary)	Electronic health record (EHR) opioid prescription data assessed quarterly 90-day periods for quarterly variables (Baseline survey date = Day 0) Baseline = Day -89 to day -0 3 months = Day 1 to day 90 6 months = Day 91 to day 180 9 months = Day 181 to day 270 12 months = Day 271 to day 360	Baseline to 3, 6 and 12 months
Examine the impact of the active interventions on depression symptomology	Patient Health Questionnaire-8 (PHQ-8)[48] (8 items; continuous)	Patient self-reported depression symptomatology at baseline, 3, 6 and 12 months	Baseline to 3, 6, and 12 months
Examine the impact of the active interventions on anxiety symptomology	Generalized Anxiety Disorder-7 (GAD-7)[49] (7 items; continuous)	Patient self-reported anxiety symptomatology at baseline, 3, 6 and 12 months	Baseline to 3, 6, and 12 months
Examine the impact of the active interventions on sleep disturbance	PROMIS Sleep Disturbance – Short Form 6a[50] (6 items; continuous)	Patient self-reported sleep disturbance at baseline, 3, 6 and 12 months	Baseline to 3, 6, and 12 months
Examine the impact of the active interventions on high impact chronic pain and graded chronic pain	High Impact Chronic Pain[4,51] Graded Chronic Pain Scale-Revised[51]	Patient self-reported pain intensity, duration, and pain-related disability	Baseline to 3, 6, and 12 months

The following **moderators** will be assessed related to MCID in pain severity at 6 months.

Moderator	**Definition**	**Data Source**
Sex	Male vs. Female/Other Sex at birth as reported by subject; assessed using HEAL CDE Demographic question	Patient self-report at baseline
Age	<65 vs. ≥ 65 years old	EHR data
Race/Ethnicity	White/Non-Hispanic Black or African American/Non-Hispanic, Hispanic Other	Patient self-report at baseline

Moderator	Definition	Data Source
Rural/medically underserved residency	Urban vs. Rural/medically underserved Rural is defined as subject's resident Census Tract corresponds to US Census 2010 Rural-Urban Commuting Area (RUCA) Codes 4, 5, 6, 7, 8, 9 or 10 (*https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/*) Medically underserved is defined as subject's resident Census Tract corresponds to HRSA-designated primary care or mental health geographic or geographic high needs health professional shortage area (*https://data.hrsa.gov/tools/shortage-area/hpsa-find*)	EHR patients' geocoded data extracted at baseline
Multiple non-malignant musculoskeletal pain conditions	1 pain cluster vs. >1 pain cluster > 1 pain-related ICD-10 diagnosis corresponding to more than one (>1) of the non-malignant musculoskeletal chronic pain condition clusters developed for the National Pain Strategy chronic pain condition clusters[52] 1. Back pain 2. Neck pain 3. Limb/extremity pain, joint pain, and arthritic disorders 4. Fibromyalgia 5. Headache 6. Orofacial, ear, and temporomandibular disorder pain 7. Musculoskeletal chest pain 8. General pain subcategory of the Other painful conditions cluster	EHR data; diagnoses in patient's EHR extracted at baseline for prior 360 days
Mental health mood disorders	ICD-10 diagnosis for depression and/or anxiety diagnosis	EHR data; diagnoses in patient's EHR extracted at baseline for prior 360 days
Negative social determinants of health (SDH)	Negative SDH/existing need vs. No SDH need Patient endorses need in one or more of the following domains: 1. Financial Resource Strain (1 item) 2. Food Insecurity (2 items) 3. Transportation/Access Needs (2 items) 4. Housing Instability (3 items)	Patient self-report at baseline

The following **mediators** will be assessed related to MCID in pain severity at 6 months.

Mediator	Brief Description of Measure	Measured By
Pain catastrophizing	Pain Catastrophizing Scale (PCS)– Short Form 6[53] (6-item; continuous)	Patient self-report at baseline and 3 months
Pain self-efficacy	Self-Efficacy for Pain Management subscale of the Chronic Pain Self-Efficacy Scale[54] (5-item; continuous)	Patient self-report at baseline and 3 months
Perceived support	2 items developed in UG3 phase	Patient self-report at notification of randomization and 3 months

3.5 Qualitative Evaluation Objectives

Qualitative Evaluation Objectives	Measured By	Time Frame during the 4-year UH3 study period
Understand health system issues, including adaptations and contextual factors at the site and external levels, barriers and facilitators to intervention success and potential for adoption, sustainability, and dissemination from perspective of health care systems	Interviews with **health care system stakeholders (including referring clinicians)** using semi-structured interview guides designed to assess relevant domains.	Conducted in years 4-5 of study
Understand patient experiences of the interventions, including how they relate to treatment response, variability by site, and rurality/medically underserved residency status	Interviews with a purposeful sample of **patients who participate in the active interventions**, stratified by site, active intervention (online program vs. virtual coach-led), response to treatment, and rurality/medically underserved residency status. Interviews will use semi-structured interview guides designed to assess relevant domains. • Interviews at 3-5 months will focus on participants' experience with the intervention and intentions to change or maintain changes learned from the intervention • Interviews at 12-14 months will focus on participants' maintenance of behavioral skills practice since intervention, and changes in domains likely affected by treatment.	Conducted in years 1-3 for 3- to 5-month interviews Conducted in years 2-3 for 12- to 14-month interviews

Qualitative Evaluation Objectives	**Measured By**	**Time Frame during the 4-year UH3 study period**
Understand patient experiences related to discontinuation of the intervention	Interviews with a sample of **patients who did not complete the active interventions to which they were randomized** (but are still enrolled in the study) using a semi-structured interview guide designed to assess relevant domains	Conducted in year 1
Process evaluation of trial implementation and delivery, including barriers and facilitators to accomplishing aims, lessons learned and changes to planned activities.	Interviews with **intervention staff/health coaches** to chronicle the process of trial implementation and delivery	Conducted years 1 and 3 of study

4 STUDY DESIGN

4.1 Overall Design

This phase III, randomized, comparative effectiveness research trial will evaluate two CBT-based chronic pain treatments delivered via different remote modalities: 1) an established online, CBT-based program (painTRAINER), and 2) a centralized, virtual coach-led CBT-CP intervention. Both modalities will be compared to usual care services.

The study uses a three-arm, parallel intervention design. Participants will be recruited from the populations of four integrated health care systems which serve as the clinical sites: 1) Kaiser Permanente Georgia (KPGA), 2) Kaiser Permanente Northwest (KPNW), 3) Kaiser Permanente Washington (KPWA) and 4) Essentia Health in Minnesota, North Dakota, and Wisconsin.

4.2 Study Arms

The three study arms to which participants will be randomized for the UH3 randomized clinical comparative effectiveness trial will be: 1) The painTRAINER online, CBT-based, pain coping skills training (PCST) program, 2) Virtual CBT-CP delivered by health coaches, and 3) Usual care. See section 10 for details on study arms 1 and 2 (the active interventions).

Those randomized to the usual care arm of the study will be mailed a bound copy of the 2020 edition of the *American Chronic Pain Association Resource Guide to Chronic Pain Management.*[39]

Patients randomized to either of the active intervention arms or the usual care arm of the study can receive any pharmacologic and nonpharmacologic treatments available to them without restriction during the study period.

4.3 Study Arm Assignment/Randomization

After completion of the baseline data collection, study participants will be individually randomized in equal ratio to one of the three study arms.

Randomization will be stratified on:

Variable	**Source**
Sex	Sex from electronic health record (Male vs. Female or Other)
Pain severity score	Score on BPI-SF from baseline survey (< 7 vs. ≥7)
Clinical site	KPWA, KPNW, KPGA, Essentia
Rural/medically underserved residency	Residency geocode for Census Tract from electronic health record

Within each stratum, to contain concealment and balance randomization over time, a random permutated block design will be used with random variable block sizes of 3, 6, or 9 to ensure approximately equal accrual into the three study arms.

The TIN JHU/Tufts Lead biostatistician, in collaboration with the study Biostatistician, will develop the randomization scheme and the TIN Utah DCC will implement the scheme by developing the randomization tables, which will be provided to KP CHR for integration into the electronic data capture system.

Randomization will occur within the KP CHR-hosted electronic data capture system after baseline assessment completion.

4.4 Scientific Rationale for Study Design

An enhanced usual care study arm has been included to address the critical question: What is the incremental benefit of the study interventions over what treatments patients are already able to access to help manage their pain? This is important to understand from a research, cost-analysis, health care-implementation and dissemination perspective. The study team recognizes that those motivated to join the study have effectively expressed an interest in obtaining additional resources for helping them manage their pain so those randomized to the usual care study arm will be sent a bound copy of the 2020 edition of the *American Chronic Pain Association Resource Guide to Chronic Pain Management*. This is a detailed informational guide to medical, interventional, behavioral, pharmacological and rehabilitation therapies, that can serve as a helpful, up-to-date resource to recipients for considering a broad range of treatment and self-management options that might help with their needs.

4.5 Justification for Interventions

Online, CBT-based pain coping skills training (PCST) program. Multiple meta-analyses support the efficacy of web-based CBT-CP interventions for improving pain and pain-related impairment.[32,55,56] Although overall effect sizes are modest, these reviews suggest the potential impact of these treatment approaches with respect to lower costs and greater safety than pharmacologic pain treatments. painTRAINER has been shown to be effective in a number of studies with high completion rates compared to other studies.[57-59] painTRAINER uses a novel approach by incorporating the expertise of experienced CBT-CP clinicians into the program's decision rules (tailoring algorithms) and knowledge database to retain critical therapeutic features of in-person CBT-CP.[60] In a randomized control feasibility trial of painTRAINER, participants demonstrated increases in self-efficacy from baseline to post intervention compared with the control group (effect size d=0.43), and women who completed the program had reduced pain compared to those in the assessment-only control condition (effect size d=0.33). The study sample included those who might be considered to have significant barriers to using online programs, including older adults (mean age of 68, range 38-90 years), minorities (35% African American), and people largely from rural, low-income areas. Some had little computer experience, and many had lower education levels (29% with high school education or less). Importantly, 93% of participants agreed the program was easy to use, and 91% completed all 8 sessions, a much higher rate than for most online interventions, and many in-person CBT-CP interventions. Overall, pain levels were mild to moderate in the feasibility trial sample, limiting benefits and indicating a need for more rigorous screening to target persons with high impact chronic pain. Screening procedures for the RESOLVE study are designed to ensure that patients in the trial have greater potential for clinical benefit (i.e., they report their pain as more disabling).

Virtual coach-led CBT-CP (telephone/video). Large trials have demonstrated clinically meaningful benefits of telephone-based CBT-CP for pain-related outcomes in the context of multicomponent interventions.[30,61,62] In a trial with 442 patients, evaluating telephonic CBT-CP and graded exercise for treating chronic widespread pain (an often treatment-resistant pain variant), telephonic CBT-CP was associated with substantial, statistically significant improvements in patient global assessment at 6- (odds ratio [OR], 5.0; 95% confidence interval [CI] 2.0 to 12.5) and 9-month (OR, 5.4; 95% CI 2.3-12.8) follow-ups.[30] The PPACT trial used substantial telephone-based CBT-CP delivery for patients experiencing barriers to in-person treatment. This care was highly acceptable to patients and feasible for master's-level, trained clinicians to reliably deliver. Finally, KPWHRI has a long history of developing successful and highly deployable telephone interventions with national uptake to provide behavioral treatment for depression and smoking.[28,29,63-67] Two small trials of telephonic CBT-CP had negative results: one was markedly underpowered and the other tested an intervention that did not emphasize behavioral activation,[68,69] deficiencies which will be addressed in the RESOLVE virtual intervention. Although this arm of the trial was initially planned as a primarily telephone-based intervention, following the Covid-19 outbreak, the health care systems in which this study is being conducted, like many across the country, are pivoting towards remote delivery of health care.[35] In this rapidly evolving treatment landscape in the participating, video-visits are preferred to telephone-visits because they are widely seen to be more satisfactory for patients given the better approximation of in-person visits as well as the additional utility of being able to share materials and see face and body language (Permanente Medicine staff communication, 4/16/20). Given that these video visits are quickly becoming the standard of care, together with findings from our pilot intervention that highlighted limitations of discussing key CBT-CP tools without being able to visually share, video visits when available and acceptable for patients will be provided.

4.6 End-of-Study Definition

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred. Therefore, the study will be complete when the last participant has completed their 12-month follow-up assessment and any scheduled qualitative interviews which will occur up to 14 months follow-up from study randomization.

5 STUDY POPULATION

5.1 Participant Inclusion Criteria

This study will primarily employ a population-based recruitment approach in which the individuals who are invited/recruited to potentially participate in the study will be identified based on the following electronic health records (EHR)-based criteria. In addition, health care providers can refer patients to the study; however, any patient referred must meet the same criteria described below.

Individuals must first meet these EHR-based criteria in order to be invited to be screened for participation.

1. Active/enrolled in one of the 4 participating integrated health care systems at the time of query and for the prior 360 days
2. Age 18 years or older (based on date of birth documented in EHR)
3. English speaking or do not need interpreter services
4. Have at least one [at Essentia] or at least two which are >60 days apart [at KP sites] outpatient pain-related health care encounter with nonmalignant musculoskeletal pain diagnoses [as determined by ICD10 codes for any of the following: back- neck-, limb/extremity-, joint-pain, arthritic disorders, fibromyalgia, headache, orofacial/ temporomandibular pain, or musculoskeletal pain][52] within the past 360 days
5. Do not have an encounter for surgery related to common musculoskeletal pain conditions (e.g., joint replacement, spinal fusion, carpal tunnel release surgery) [as determined by CPT and/or ICD-10 codes] within the past 60 days
6. Do not have two or more separate encounters with a malignant cancer diagnosis other than non-melanoma skin cancer [as determined by ICD-10 codes] within past 60 days
7. Do not have ICD-10 code(s), CPT code(s) or department/provider encounters indicating receipt of hospice or other palliative care within the past 360 days
8. Do not have ICD-10 codes indicating severe cognitive impairment precluding participation in a behavioral/ lifestyle change program

[Note: At the KPWA site only, one additional EHR-based exclusion criterion will be applied, which is: Do not have ICD-10 codes indicating opioid use disorder (OUD). This criterion is being applied because there is another HEAL study being conducted at KPWA that focuses on treating individuals with pain and OUD specifically.]

Individuals who meet the above EHR criteria will be invited to respond to screening questions and must meet the following inclusion criteria:

1. Have high-impact chronic pain (as indicated by self-report of having pain on most or every day in past 3 months and pain limiting life or work activities on most or every day in past 3 months)[4]
2. Have persistent pain (as indicated by self-report PEG score of ≥ 12)
3. Be able to participate in either of the active interventions (i.e., have internet and phone access required for accessing treatments)

5.2 Participant Exclusion Criteria

Individuals screened who meet the inclusion screening criteria (and the initial EHR criteria described above) cannot endorse any of the following exclusion criteria:

1. Have received CBT for pain or pain-related psychoeducation or behavioral skills training within in the past 6 months (in-person, by phone or videoconference, or online)
2. Currently receiving or will be starting CBT for pain or pain-related psychoeducation or behavioral skills training in the next month (in-person, by phone or videoconference, or online)
3. Currently receiving or will be starting inpatient or intensive outpatient services for substance use disorder in the next month
4. Have a planned/scheduled surgery in next 12 months related to pain condition

6 RECRUITMENT PROCEDURES AND RETENTION STRATEGIES

6.1 Recruitment of Patients

Each of the 4 sites will be responsible for recruiting and enrolling approximately 595-625 patients per site but the final number will vary slightly across sites. In order to reach the overall study target for number randomized within the study timeline, some sites may enroll more than others (i.e., Essentia and KPGA vs. KPWA). [Note: The study aims to randomize 2,331 individuals (at least 777 per arm) and, as such, the number needed to enroll may be larger than the 2,500 target as not all who consent/enroll go on to be randomized.] Study activities from recruitment through completion of baseline survey will be completed by each site for their population of patients.

For recruitment, each site will query their EHR data warehouses to identify a sample of patients who meet the EHR-based inclusion criteria on a set frequency. The sample of patients will be stratified by urban vs. rural or medically underserved residence, based on the individuals' resident Census Tract/geocoded data in the EHR. The table below provides definitions to be used for these categories.

Urban	Rural or Medically Underserved (MUA)
Urban is defined as subject's resident Census Tract corresponds to US Census 2010 Rural-Urban Commuting Area (RUCA) Codes 1, 2 or 3 (*https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/*)	Rural is defined as subject's resident Census Tract corresponds to US Census 2010 Rural-Urban Commuting Area (RUCA) Codes 4, 5, 6, 7, 8, 9 or 10 (*https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/*) Medically underserved (MUA)is defined as subject's resident Census Tract corresponds to HRSA-designated primary care or mental health geographic or geographic high needs health professional shortage area (*https://data.hrsa.gov/tools/shortage-area/hpsa-find*)

Then, a random sample of approximately 500-700 patients per month per site will be generated, with adjusted sampling for rural residency to ensure at least 20% in either the urban or rural/MUA subgroup at each site. Specifically, individuals who reside in rural or medically underserved areas will comprise 30-50% of the overall RESOLVE study population. Each site will have at least 20% enrollment in either subgroup (urban vs. rural/MUA) to enable sufficient sample size for subgroup analyses.

Patients in the random sample will be mailed a recruitment letter and brochure which includes: a description of the study, instructions for how to call a research staff person to complete the screening survey by phone or complete it online, and select elements of informed consent, including a clear statement of the ability to opt out of further contact by calling the site-specific study telephone number. Finally, the letter states that patients might be contacted by phone in the following weeks to participate in the study if they have not called to opt-out of further contact or gone online to complete the screening survey. Each site, as feasible/allowable, will also send

a recruitment email in follow-up to the mailing to patients in the sample who have an active email address. See section 7 for a complete description of the screening process.

The population-based recruitment process described above will be the primary method for identifying potentially eligible patients for this trial. A secondary method will be by health care provider or self-referral. Health care providers, including primary care providers, physical therapists, health and wellness education staff, and others within the participating health care system, will be given information about the study via multiple methods such as staff messaging, staff intranet resources, and outreach/education at existing clinic and provider meetings. For patients who agree, health care providers will be able to electronically route a referral to a study staff member either within the EPIC EHR (that is linked to the patient's record), by staff message, or by leaving pertinent information (patient name and health record number for retrieval of contact information) on a study-specific voicemail, accessible only by select study staff. Then, study staff would ensure that the patient meets the EHR-based inclusion criteria (by analyst executing a pre-developed program). Health care providers will also be able to provide patients with information about the study (brochure) and the number of the study-specific confidential voicemail so that patients can self-refer to the study or patients may obtain information about the study on their own. Study staff would contact patients who self-refer, obtain their permission to assess their EHR-based eligibility, and then the analyst would execute the pre-developed program. If the person does not meet the EHR-based inclusion criteria, the study staff person will follow-up with the patient by phone or mailed letter to explain this and call or send a staff message back to the referring provider informing them. If the person does meet the EHR-based inclusion criteria, the study staff member will notify the referring clinician of this (if applicable), and the participant will then be mailed a recruitment letter and follow the same process as described above for those identified through the EHR query.

In addition, a subset of approximately 100-120 patient participants will be invited to complete interviews as part of the qualitative evaluation. Approximately 20 of these interviews will be conducted once early in the launch of the UH3 trial with select participants randomized to the active intervention arms who drop-out of intervention participation early (i.e., only complete 2-5 sessions) or are less consistent in their engagement with intervention activities; these individuals have not withdrawn from the study. The remaining approximately 100 interviews will be conducted with a subset of individuals randomized to the active intervention arms; sampling for these interviews will be based on 1) clinical site, 2) active intervention arm, 3) treatment response at 3 months (based on 3-month BPI-SF assessment), and 4) rural/medically underserved vs. urban residency. This larger subset of interviewees will be recruited to complete interviews at approximately 3-5 months and again at 12-14 months following randomization. Individuals who are recruited for interviews will have endorsed their willingness to potentially participate in the interviews on their baseline survey. The Utah Data Coordinating Center (DCC) will work with the study team to provide a report of individuals to enable stratification for interview sampling based on the criteria listed above. These individuals will first be mailed a letter describing the goals of the interview, the process, and who to contact on the study team if they are interested. Finally, the letter states that patients might be contacted by phone in the following weeks about participating in an interview if they have not called to opt-in or out of participating. Study staff will follow-up by phone and/or email to schedule interviews.

6.2 Recruitment of Stakeholders for Qualitative Evaluation

Recruitment of health care system stakeholders and referring clinicians**.** Up to 20 health care system stakeholders will be interviewed, including select clinicians, from KPGA, KPNW, KPWA, and Essentia in the areas of quality improvement, primary care, and/or pain management. Stakeholders and clinicians will be identified by the research investigators at each site in collaboration with health care system study partners based on their expertise and roles within the health care system as it pertains to pain management / service delivery. Approximately 8 interviews will be with health care system leadership and up to 12 interviews with referring clinicians across the health care systems if this option is used routinely. Targeted stakeholders and clinicians will be sent a one-page fact sheet, which will include the consent elements that are pertinent to the interview process, and invitation email from the site PI or co-I, inviting them to do an interview. If the individual agrees, they will be connected to the KP CHR qualitative research team members who will schedule the interview.

Recruitment of intervention / health coaching staff for qualitative evaluation.
All (approximately 12) of the health coaching staff [centralized at KPWHRI (KPWA) and KP CHR (KPNW)] who deliver the virtual intervention and the intervention staff who support participant engagement with painTRAINER will be invited to complete study interviews with members of the qualitative research team at KP CHR describing their experiences delivering the study protocol and working with participants in the active intervention arms of the study. Intervention staff / health coaches will be free to decline these interviews and will be told that their names will not be attached to any data derived from this interview data.

See section 8 for a description of the consent processes for these individuals.

6.3 Retention Strategies

Retention of patients. The following strategies will be used to maximize follow-up rates: 1) allow participants to complete assessments using the mode they prefer (online, by telephone, or a mailed survey); 2) confirm and update contact details at each survey contact; 3) use standard tracking or EHR/administrative records to locate persons who move; and, 4) provide incentives that adequately compensate subjects for the time spent completing assessments (see table below) and increase as subjects continue in the study. Specifically, participants will receive $25 at baseline and $30, $35, and $40 at each follow-up time point respectively, if they complete by paper or phone, and $5 more at each follow-up time point for completing by web (with the rationale that the additional funds compensate for the cost of broadband necessary to complete the assessments online).

	Time Point			
Completion Mode	Baseline	3-month	6-month	12-month
Phone	$25	$30	$35	$40
Paper	N/A	$30	$35	$40
Web	$25	$35	$40	$45

Patients who participate in the qualitative evaluation will receive $30 for each interview completed.

7 ELIGIBILITY SCREENING

Patient screening process. Upon receiving the recruitment letter and brochure or recruitment email (if applicable at the site), patients can choose to complete the eligibility screening survey by web or call study staff at their specific clinical site to complete the questions by phone. In addition, as described in section 6.1 on recruitment, study staff will also conduct outreach calls to conduct eligibility screening with individuals who do not complete the screening by web or call in on their own. The specific procedures for each screening mode are described below.

The eligibility screening survey will take approximately 10-15 minutes and assess the following eligibility criteria:

- English speaking
- Do not have a cognitive impairment severe enough to preclude participation in study
- Be able to participate in either of the active interventions (i.e., have email, internet and phone access required for accessing CBT-CP treatments).
- Meet the following definition of high impact chronic pain.
    - Experience pain on most or every day of the past 3 months
      AND
      Pain limits life or work activities most or every day of the past 3 months
- Score ≥12 on the 3-item PEG assessment
- Not currently receiving, about to start, or have received in the past 6 months CBT for pain or similar pain-related psychoeducation or behavioral skills training
- Not currently receiving or about to start substance abuse treatment services (inpatient or intensive outpatient)
- Not planning/scheduled for surgery related to pain condition in next 12 months

Screening by web. Patients who choose to complete the eligibility screening by web will either go to the study website and access the screening survey by entering the unique survey code from their recruitment letter or click on the unique survey link provided in the recruitment email (if applicable for their site). As described above, the web-based screening survey should take approx. 10-15 minutes to complete. Upon completion of the screening survey, patients will be informed whether they are eligible to participate in the study or not.

If ineligible, they will be presented with a closing webpage thanking them for their time and interest, briefly explaining the reasons for ineligibility, and giving them the site study contact phone number if they have further questions.
If eligible, they will be able to complete the informed consent and baseline survey via web, as described in section 8.

Screening by phone. Patients who opt for phone screening will complete the 10-15 minute screening survey with the health care system research staff supporting telephone screening. If ineligible, they will be informed during the call and able to ask questions. If eligible, they will be given the options of 1) completing the informed consent immediately by phone as well as the baseline survey, or 2) being contacted at a later time to complete the informed consent and baseline survey by phone.

8 INFORMED CONSENT PROCESSES

8.1 Informed Consent of Patients

Electronic Health Records (EHR)-Based Population Screening and Recruitment

- No consent is required to *conduct the population-based screening and recruitment process* described in section 6.1, which involves each site querying existing administrative EHR records to extract PHI limited to the information necessary for determining potential eligibility and conducting further screening.
- This also applies (no consent required) to the patients who are *referred by their health care provider* to be screened for study eligibility. The provider will discuss the study directly with the patient; if s/he agrees, a referral will be electronically routed to a study staff member who will assess whether the patient meets the EHR-based inclusion criteria, as also described in section 6.1.
- A waiver of the documentation of informed consent will be obtained for *patients who self-refer to the study* after receiving the brochure from their provider or obtaining the information on their own. Because these individuals will contact study staff directly, it is feasible to obtain verbal consent to verify their potential eligibility based on the EHR-based inclusion criteria. The provider recruitment brochure and EHR eligibility consent phone script address the elements of consent that are applicable to this screening process. In addition, patients will agree to the use of their PHI to assess their eligibility.

Eligibility Screening Survey

A waiver of the documentation of informed consent will be obtained in order to conduct the eligibility screening survey. All potentially eligible patients (based on the EHR data) will have been mailed a recruitment letter and brochure, as described in section 6. Upon receiving the recruitment letter and brochure, patients can choose to go to the website to complete the eligibility screening survey or call their clinical site to complete the eligibility screening survey by phone. If a potentially eligible patient does not complete the screening survey by web or proactively call the study on their own, study staff will attempt to reach them by phone, as described in section 6.1 on recruitment.

Screening Survey by Web: If a patient goes to the website to complete the screening, before they are presented with the opportunity to answer the eligibility questions, they will be presented with a written statement that contains the elements of informed consent that are applicable to the screening process. In addition, the statement will provide a phone number to call research staff if they have questions. After being presented with this statement to read, patients will be asked to electronically endorse their consent to complete the eligibility screening before they can answer the eligibility questions.

Screening Survey by Phone: If a patient calls into the study phone line or is called by study staff after receiving the recruitment letter and brochure, a staff member will review the same information that is presented to patients who go to the website using a script that contains the elements of informed consent that are applicable to the screening process. In addition, the research staff will ask patients if they have any questions. After reviewing this information, patients will be asked to verbally confirm their consent to proceed with the

eligibility screening and their response will be documented by study staff in the electronic data capture system. Only after providing verbal consent will, they be asked the eligibility screening questions by the research staff.

Study Enrollment

A waiver of the documentation of informed consent will be obtained in order to conduct the informed consent process for the study by phone (consent obtained verbally) or by web (electronic endorsement of consent). All participants are provided with information containing all elements of informed consent, as they apply to all parts of the study, however participants will not document consent with a signature.

If a patient is determined to be eligible based on the screening survey, s/he can proceed with the informed consent process by web or phone during the same encounter as the screening survey. Or, if a patient would prefer to conduct the informed consent process at a later time s/he can return to the website later to complete it electronically or schedule a time to complete it by phone with a study staff member.

Website: If a patient is determined to be eligible based on the screening survey completed by web, s/he will be able to continue with the informed consent process. Patients will be directed to download and read (via PDF link) the combined master information sheet and site-specific information sheet, which includes all elements of consent and HIPAA authorization information and encouraged to keep it for their records. They will also be directed to call their site's study-specific phone line if they have any questions before they decide to participate. Patients will be asked to electronically endorse their consent and HIPAA authorization. After completion of the consent process by web, participants will be mailed a copy of the information sheet for their records. In addition, sites may follow-up by phone with individuals who enrolled by web in order to briefly welcome them to the study and clarify next steps.

Phone: If a patient is determined to be eligible based on the screening survey completed by phone, s/he will be able to continue with the informed consent process. The study staff person will review the elements of consent and HIPAA authorization information which are contained in the study information sheet, using the consent phone script. While on the phone, the staff person will direct the patient to the study website where the combined master information sheet and site-specific information sheet can be downloaded and reviewed by the patient as the staff person explains/reviews its content. Verbal consent will be obtained as well as verbal HIPAA authorization. After completion of the verbal consent process, participants will be mailed a copy of the information sheet for their records.

For the subset of individuals who are recruited to complete interviews, they will have consented to the interview as part of the study's informed consent process. When the KP CHR study team member calls these individuals at the pre-scheduled time, s/he will confirm that the individual

received the information sheet and confirm that the interviewee agrees to have the interview recorded before any recording begins.

8.2 Informed Consent of Stakeholders and Staff

As noted in section 6.2, which describes recruitment strategies, stakeholders will have received an email invitation with a one-page fact sheet attached, which includes the consent elements that are pertinent to the interview process prior to agreeing to schedule an interview. When the KP CHR study team member calls these individuals at the pre-scheduled time, s/he will ask if the stakeholder interviewee has received the fact sheet and if s/he has any questions before the interview commences. In addition, the KP CHR study team member will confirm that the stakeholder interviewee agrees to have the interview recorded before any recording begins. Consent will not be obtained from the individuals who choose to complete a stakeholder interview. They are given a fact sheet, containing elements of consent, as described above. The interview itself focuses on organizational processes, and although the stakeholder does share opinions and perspectives on organizational topics, they do not share personal or protected health information. This is an appropriate consent procedure given the minimal risk to the stakeholder posed by the interview and the fact that the interview involves discussing organizational topics commonly discussed in work-related meetings. In addition, due to the professional focus of the interviews (and often the organizational prohibitions restricting such individuals from accepting an incentive), stakeholders will not be paid an incentive for their participation.

Informed consent process for intervention / health coaching staff. The intervention / health coaching staff will be given a one-page fact sheet, which includes the consent elements that are pertinent to the interview process prior to agreeing to schedule an interview. They will be informed that they can refuse participation with no impact on their work. When the KP CHR study team member calls these individuals at the pre-scheduled time, s/he will ask if the interviewee has received the fact sheet and if s/he has any questions before the interview commences. In addition, the KP CHR study team member will confirm that the interviewee agrees to have the interview recorded before any recording begins. Consent will not be obtained from the staff who choose to complete an interview based on the rationale outlined above for the stakeholders.

9 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

9.1 Discontinuation of Study Intervention

There are no criteria for the PI to discontinue the administration of the study intervention that are related to specific adverse events or serious adverse events.

There may be rare instances in which an individual decompensated (or was threatening to study staff) and was consequentially unable to continue to actively participate in a behavioral intervention of the type administered in this trial. In this event, the reason for discontinuation will be documented and an attempt to connect the participant to relevant behavioral health resources/support in their region will be made.

If a participant informs the study staff that they will discontinue participation in the intervention, staff will assess their reasons for discontinuation and determine whether the participant wants to continue with the other study activities or withdraw from the study entirely.

9.2 Participant Discontinuation/Withdrawal from Study

There are only rare circumstances under which the PI would discontinue/withdraw a participant from the study. As noted above, in the rare instance in which an individual decompensated (or was threatening to study staff) and was consequentially unable to continue to complete study assessments, the reason for discontinuation would be documented and an attempt to connect the participant to relevant behavioral health resources/support in their region. If a participant informs the study staff that they will discontinue participation in the study, staff will assess and document their reasons for discontinuation. As specified in the consent, any data collected up to the point of withdrawal will be retained.

9.3 Loss to Follow-Up

Participants randomized to the online program or virtual CBT-CP will be considered lost to follow-up after 1) they have missed 2 or more of the weekly sessions or 2) a study staff member has been unable to reach them after making multiple contact attempts (up to 7 calls or emails and 2 mailed letters) over a 4 to 6-week period.

If a participant is considered lost to follow-up for the active intervention, the individual will still be contacted per the follow-up assessment outreach process for each time point unless there is no active/working phone, email, or mailing address available for them.

10 STUDY INTERVENTIONS

10.1 Description of Interventions

Both active intervention arms are based on the same core CBT-CP program (pain-coping skills training) developed and refined by Dr. Keefe and colleagues at Duke University over the past three decades. In addition, the virtual coach-led CBT-CP coach manual and participant workbook are based on the PPACT intervention, which was tested in a large pragmatic trial led by Dr. DeBar.[70,71]

CBT is the most widely accepted, evidence-based, nonpharmacologic treatment for chronic pain and has been shown to benefit low-literacy adults in rural areas.[1,16,17] CBT-CP is based on the theory that patients' beliefs, attitudes, behavior, and coping styles play central roles in determining (mediating) the impact of persistent pain.[18]

CBT-CP effects can be maintained long after treatment ends, without the negative side effects of opioids and other pain medications and is an attractive adjunct or alternative to pharmacological treatments. CBT-CP It focuses on helps patients develop and master skills to manage pain and the disability and emotional distress associated with pain in order to improve their functioning and quality of life. CBT-CP enhances the use and perceived self-efficacy of pain coping skills that address cognitive processes (e.g., reducing catastrophizing) and behaviors (e.g., engaging in meaningful activities and goals).

The table below provides an overview of the core content for both of the RESOLVE study interventions. Both interventions include elements to enhance learning and mastery of skills that are guided by social cognitive theory (e.g., social modeling, vicarious learning),[72,73] adult learning theory (e.g., tying skills to personal goals and experiences),[74,75] principles of multimedia instruction (interactive exercises, graphics to reinforce explanations),[76] and behavior change theory[77] (e.g., behavior tracking).

Description of RESOLVE Intervention Session Content

Session	Unique Topics/Skills*	painTRAINER	Virtual Coach-Led CBT-CP
1	Rationale & Foundation of Self-Care/Relaxation Skills	✔	✔
2	Review relaxation skills (Progressive Muscle Relaxation and Mini-practice)	✔	✔
3	Activity / rest cycling	✔	✔
4	Pleasant activity scheduling / Negative automatic thoughts	✔	✔
5	Negative automatic thoughts / Coping thoughts	✔	✔
6	Pleasant imagery / distraction	✔	✔
7	Problem-solving	✔	✔
8	Monitoring for maintenance	✔	✔

*Each session includes goal setting (Session 1); goal review and refinement (sessions 2-8)

10.1.1 painTRAINER

Overview. painTRAINER is an online, 8-session, pain coping skills training program (PCST) based on cognitive behavioral therapy (CBT). Each session takes 45-60 minutes to complete and provides interactive training in one or more evidence-based pain-coping skills.[59] Participants complete sessions on their own, in a set order, and are encouraged to complete one session per week. Session completion is flexible – participants can close a session before completing it and later resume where they left off. They can also go back to review completed sessions or sections of completed sessions (e.g., an audio recording of a skill practice, or instructions on how to use a skill). The sessions are led by a recorded "virtual coach" who speaks directly to users. Thus, content is provided in audio to minimize reading and facilitate program completion for low-literacy patients. painTRAINER was designed to include features of therapist delivered PCST, while providing training in an easy-to-use format that includes animated demonstrations, interactive exercises, working through common barriers to behavior change/skills practice, and tailored feedback to reinforce learning.

Onboarding and Registration. Following randomization, participants who are assigned to painTRAINER are mailed materials that include instructions for registering for the program, unique login information, a participant workbook, and study team contact information (in case of questions or technical difficulties). Approximately a week after the materials are mailed, study staff call participants to "onboard" them to the program. This entails providing a verbal overview of the program and making sure participants register and are able to access/log into painTRAINER. Study staff follow specified guidelines to complete the onboarding call which include suggested language/scripting. [Note: On 08/09/21 VUMC IRB approved revised onboarding guidelines which added motivational interviewing-based language. This language was to be used, as feasible.] The primary goal of the onboarding call is to ensure that participants register and have no technical difficulties. The inclusion of MI-based language allows the staff person doing the onboarding to ask participants to consider potential barriers to participation and how they might plan in advance to overcome such challenges as well as to reaffirm their rationale and commitment to utilize painTRAINER to learn skills to manage their pain.

Ongoing Support and Engagement. After participants begin the painTRAINER program, automated email reminders are sent to practice skills and complete modules. Support is also provided by study staff if a participant is not adhering to the recommended completion schedule. Specifically, a study staff person will follow-up with a participant by phone in the following circumstances:

- It has been more than 7 days since the participant registered and session 1 has not been initiated.
- A session has been initiated but is still incomplete after more than 7 days.
- It has been more than 10 days since the most recent session completion date and another session has not been initiated.
- Sessions are being completed too quickly (3 or more sessions completed in 9 days).

Study staff utilize specified guidelines to complete follow-up calls which include suggested language/scripting. The goal of the follow-up call is to identify and resolve the reason for non-adherence.

10.1.2 Virtual Coach-led CBT-CP

Overview. The coach-led program includes 8 sessions of CBT-CP provided one-on-one via telephone or video encounters. Each session takes 60 minutes and provides interactive training in one or more evidence-based pain-coping skills. Sessions are scheduled at the participant's convenience with approximately one session per week and participants have the option of meeting with the coach by telephone only, using video conferencing or a combination of the two. The live virtual-enabled coaching provided can enhance patient motivation and engagement. This approach is likely to be especially useful for depressed or anxious patients (common chronic pain comorbidities) for whom de-activation and/or avoidance may create barriers to implementing effective pain-coping skills. Coaches providing these virtual visits are required to have at least master's-level behavioral health training and conduct coaching sessions from the study sites at KPWHRI in Seattle and KP CHR in Portland. This telehealth model of centralized behavioral health services is being widely adopted across health care systems nationally, and thus represents a critically important approach for this active arm of the study.

Onboarding. Following randomization, participants assigned to Virtual Coach-led CBT-CP are mailed materials that include a brief biographical description of their health coach and a participant workbook with handouts for the 8 sessions and materials for logging skills practice. The assigned coach calls the participant approximately one week after the materials are mailed. The primary goal of this outreach by the coach is to introduce themselves and to “onboard” the participant to the program. The onboarding call includes verifying receipt of the packet of materials and orienting the participant to the Virtual Coach-led program structure and format. Participants are informed that coaching calls are confidential, asked their preference for telephone or video coaching calls and for permission to record all coaching calls. The coach will use the onboarding call as an opportunity to respond to questions from the participant and to schedule the first coaching call. Coaches follow specified guidelines to complete the onboarding call which include suggested language/scripting.

Ongoing Support and Engagement. Coaches work with participants to schedule sessions at the most convenient time for them, with an emphasis on completing one coaching call per week for 8 weeks. Frequently, a standing weekly meeting time is identified for the 8 weeks, however there is flexibility in this schedule and coaches can accommodate scheduling challenges, as necessary. Coaches remind participants 1-2 days before a scheduled session via phone or email (based on participant preference). If a participant does not attend a scheduled call, the coach will first reach out by telephone to reconnect and reschedule the missed appointment. When reached, the coach may explore possible barriers to completing the program and work with the participant to problem-solve for any challenges, as appropriate. If the participant is not reached right away, as described in Section 9.3. multiple outreach attempts will be made over the course of several weeks, using different contact modes, including phone, email and mailed letters. (Note: In the rare circumstance that a participant cannot be reached by phone, email or letter, the coach will send a text as a last resort for outreach.)

10.2 Intervention Administration and Dosing

Both the painTRAINER program and the virtual coach-led CBT-CP sessions are intended to follow a weekly administration schedule (1 session per week over the course of 8 weeks). However, completion may vary due to the personal circumstances of the participants. The maximum intended duration for the active intervention period is 12 weeks, meaning study staff will proactively follow-up to ensure session completion during that time period. If someone has not completed all 8 sessions within 12 weeks, study staff will not do any further follow-up to encourage completion of online sessions or schedule telephonic/video sessions.

- The exception to this is when a participant is actively engaged with coaching staff and requests and is able to complete any remaining intervention sessions beyond yet close to the 12-week target. These instances will be reviewed by clinical supervisors and decisions will be made on a case-by-case basis before virtual intervention activities continue. All intervention-related contacts are documented and any that occur after the active intervention period can be identified/flagged for analytic purposes.
- Note: painTRAINER remains open to participants and access cannot be restricted after 12 weeks. However, the program automatically collects data on any logins that occur after the 12-week period and information related to completion of sessions after the intervention period may be used analytically.

Participants are considered to have received a full dose of the interventions if at least 75%, or 6 of the 8, sessions have been completed.

10.3 Masking and Measures to Minimize Bias

It is not feasible for participants to be masked to treatment arm assignment due to the behavioral nature of the intervention. The PI and select Co-Investigators and study staff who are involved in the oversight and delivery of the interventions will also be aware of treatment assignment. Outcome assessors will be masked to treatment assignment. Assessments completed on paper will be entered by research staff who are blinded to the randomization status of the study participants.

10.4 Study Intervention Fidelity Monitoring Procedures

Training and monitoring intervention fidelity for virtual coach-led CBT-CP. Maximum generalizability and relevance to community providers will be addressed by applying the Treatment Fidelity Workgroup of the NIH Behavioral Change Consortium[80] framework to ensure interventions are delivered as intended. Treatment fidelity is maximized by use of fidelity induction and monitored by fidelity assessment. In this study, fidelity induction will be achieved by the use of proactive strategies including: a formal structured orientation and training process for health coaches, use of standardized treatment manuals and training materials, repetition and practice of training skills, and adequate achievement of proficiency in core skills before health coaches start to work with study participants.

All coaches will receive training prior to conducting treatment sessions with study participants. The initial training will consist of approximately 16 hours of didactic and experiential coursework conducted by Drs. Balderson, DeBar, Murphy and/or Keefe. Interventionists will be provided with the treatment manual and the treatment strategies will be taught through didactic instruction, recorded illustrations of techniques from model cases, and role-play of common

scenarios. Health coaches will complete two role plays of the eight intervention sessions, one as a coach and one as a participant (i.e., 16 mock sessions total). Upon completion these initial training activities, a health coach will be assigned active study patients.

During the first 4 months post-completion of training, recordings from at least two completed encounters for each session number from the coaches' first 5 patients will be reviewed and scored for proficiency by at least one of the following individuals: Drs. Balderson, DeBar, Keefe, Murphy and/or Ms. Firemark. For each encounter that is reviewed, two assessments will be completed: 1) Fidelity to Session Content 2) Fidelity to Cognitive-Behavioral Therapy Treatment (using a modified version of the *VA Cognitive Behavioral Therapy for Chronic Pain Therapist Rating Scale*).[20] During this acute phase of session review, written and/or verbal feedback is provided to coaches on a weekly basis.

After health coaches reach proficiency in the delivery of each session (based on scored recordings), ongoing ratings of recorded sessions will be conducted by one or more of the following individuals: Drs. Keefe, Balderson, DeBar, Murphy and /or Ms. Firemark monthly as coaches gain experience with the intervention. Ongoing telephonic treatment protocol adherence will be monitored via multiple methods that include: 1) therapists' completion of a self-assessment of protocol fidelity adherence after every session using the session-specific Fidelity to Session Content checklists, 2) review and scoring of recorded sessions with patients using the Content checklists and the Cognitive Therapist Rating Scale, and 3) coach request for recording review for any challenging session or sessions viewed as potentially problematic in treatment fidelity. Identified deviations from the treatment protocol will be addressed immediately by providing any coach identified as having poor adherence to the intervention manual with more intensive supervision and monitoring until adherence criteria is re-established. This is consistent with how this would occur in everyday clinical care. This approach was used successfully in previous CBT-CP studies.[25,71,81-83]

10.5 Concomitant Therapy

As noted in the exclusion criteria, study participants cannot at the time of study enrollment or in the 6 months prior receive Cognitive Behavioral Therapy (CBT) for pain or a similar psychoeducational skill-based training for pain (nor indicate that they have scheduled to begin such treatment). However once enrolled, participants can receive any pharmacologic or nonpharmacologic treatments available to them without restriction. At each study assessment (3-, 6- and 12-month follow-ups), participants' use of CBT for pain or a similar psychoeducational skill-based training for pain (in-person, by phone or via online or App-based programs) will be assessed.

11 STUDY ASSESSMENTS AND PROCEDURES

Section 8 describes the informed consent process in detail. The consent process will occur prior to initiation of the baseline survey but ideally during the same phone encounter or web survey session as the screening.

11.1 Baseline Assessment

Patient baseline assessment. Patients who consent to participate in the study will be asked to complete the baseline assessment either by phone or online immediately following the informed consent process. The baseline assessment will include the measures described in section 3.1. In addition, the baseline assessment will confirm contact information, collect preferences for the administration mode of follow-up assessments, and assess subjects' willingness to potentially participate in the interviews as part of the qualitative evaluation. It is expected that the informed consent and baseline assessment will take approximately 45-60 minutes.

11.2 Follow-Up Assessments

Patient assessment at the time of notification of randomization. At the time that participants are mailed the materials notifying them of their study arm assignment, they will also be mailed a brief paper survey and a pre-posted return envelope. The paper survey will assess the participants' perceived support of the intervention to which they have been assigned and will serve as the baseline assessment of this potential mediator variable. The paper survey will take no more than 5 minutes to complete. (Note: This assessment is offered only by paper due to the fact that it is mailed with the other materials related to randomization notification and logistically it is most feasible to administer this way at this particular time point.)

Patient follow-up assessments at 3-, 6- and 12-months. Based on the preference for survey administration mode (online, phone or paper) indicated at the time of the baseline assessment, participants will initially be sent the follow-up survey via their preferred mode. (Note: At any point during the study, a participant can change their preferred survey mode.) The protocol for follow-up with non-responders within the assessment window will employ the other modes of contact in order to maximize the opportunity to reach participants. For example, subjects who prefer email contact for the assessments will also be contacted by phone if they do not complete the assessment using the web link in the emails within a set period of time. Each follow-up assessment will take approximately 30 minutes to complete. The specific protocol for contacts related to follow-up assessments is described in the study's operating procedures.

11.3 Qualitative Interviews

Patient interviews. A subset of approximately 100 patients will be invited to complete two approximately one-hour long interviews by phone at approximately 3-5 months and 12-14 months post-randomization. A different subset of 20 individuals who do not complete the interventions but are still enrolled in the study (see details related to selection criteria for these interviews in section 6.1) will complete one interview approximately one-hour in length by phone. Interviewers will use semi-structured interview guides for all patient interviews. These interviews will be audio-recorded.

Stakeholder and referring clinician interviews. The stakeholder interviews will be approximately an hour in length and conducted primarily by phone using a semi-structured interview guide; in the instance that a stakeholder is unable to complete the interview in one encounter due to scheduling issues that may arise which allow less an hour for the phone call, follow-up to complete questions may be conducted by phone or email. These interviews will be audio-recorded.

Intervention staff / health coach interviews: Qualitative research team members will attempt to conduct interviews with all (approximately 12) of the intervention/health coaching staff. These interviews will be approximately one-hour in length and conducted twice (early in study implementation and later); they will be audio-recorded.

12 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

12.1 Definition, Classification and Reporting of Adverse Events

12.1.1 Definition of Adverse Events (AEs)

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal signs, symptoms, or diseases, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Because the RESOLVE study involves minimal risk and the study population includes patients with high impact chronic pain, who have fluctuating physical and emotional symptoms as part of the natural course of their condition, such symptoms will not be systematically solicited as part of the trial.

AEs will be identified if:

- Participants proactively contacts study staff at any time to self-report an AE;
- Participants happen to self-report an AE during a regular study contact with intervention or study staff; or
- Participants attribute study withdrawal or dropout to unfavorable medical / health-related issues.[84]

AEs will not be solicited uniformly from all study participants, as capture of these events will be biased by study arm (i.e., telephone CBT-CP participants will have greater interaction with study staff by phone and more opportunity to self-report these symptoms and events).

AEs will be entered by study staff into the Utah/DCC REDCap AE database at the time of reporting by the participant.

12.1.2 Definition of Serious Adverse Events (SAEs)

For this comparative effectiveness trial, a serious adverse event (SAE) is defined as an event that:

- Results in death during a patient's active participation in the trial.
- Results in inpatient hospitalization during a patient's active participation in the trial. (Planned hospitalization scheduled before the enrollment of a study participant is not an SAE.)

Because the patients who participate in the RESOLVE study will be older and have co-morbid health conditions, it is expected that subjects will experience inpatient hospitalizations, which are unrelated to study participation, during the course of the study. In addition, it is expected that deaths, which are also unrelated to study participation, might occur among study enrollees based on prior studies. Specifically, in the study PI's recently completed pragmatic trial, PPACT, which provided an intensive in-person behavioral intervention and enrolled 850 patients with chronic pain, there were 12 deaths during the study, all unrelated to study participation, and 287 hospitalizations (116 for intervention participants and 171 for usual care).

SAEs will be systematically assessed every 6 months for active study participants based on electronic health records (EHR) data.

- Each clinical site will query active participants' electronic health records data every 6 months (in alignment with the DSMB meeting schedule) to identify any deaths or hospitalizations throughout the interval of active participant enrollment in the trial.
- An independent physician within each health care system/clinical site will conduct a chart review for each death and hospitalization to assess its potential relatedness to study procedures and interventions.
- The summary of SAEs and findings of these reviews will be submitted to the DCC.

In addition to the semi-annual EHR queries, SAEs may be identified by participant self-report. If this occurs, the event will be documented and reviewed by the independent physician as part of the semi-annual review described above.

12.1.3 Definition of Adverse Events of Special Interest (AESI)

This protocol will not collect solicited adverse events of special interest (AESI). There is no clinical or empirical basis for hypothesizing that either of the active interventions would increase risk of AESIs. In addition, the unequal contact with study staff among participants in the three study arms inherently results in differential opportunities for ascertainment of "events." Therefore, between-group comparison of adverse events reported to or discovered by study staff would be biased and hence not meaningfully interpretable or actionable.

12.1.4 Severity of Adverse Events

For an AE, the following guidelines will be used to describe severity:

- Mild – event does not generally interfere with usual daily activities and/or does not require medical care.
- Moderate – event interferes with usual daily activities and/or requires self-medical care or outpatient medical care.
- Severe – event interrupts usual daily activities and/or requires inpatient medical care or medical care with overnight stay in hospital observation services.

12.1.5 Relationship to Research Participation

For an SAE, the following guidelines will be used to describe relatedness to study procedures and study interventions:

- Related – There is clear evidence to suggest a causal relationship between the study procedures or study interventions and the SAE, and other possible contributing factors can be ruled out.
- Possibly Related –There is a reasonable possibility that the study procedures or study interventions caused the SAE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures or study interventions and the SAE.
- Not Related – There is not a reasonable possibility that the study procedures or study interventions caused the SAE, there is no temporal relationship between the study procedures or study interventions and event onset, or an alternate etiology has been established.

12.1.6 Expectedness of Adverse Events/Serious Adverse Events

An AE/SAE will be considered unexpected if it occurs in one or more subjects, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in Section 2; or
- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

12.1.7 Reporting Procedures for Adverse Events/Serious Adverse Events

Any AEs self-reported by participants to study staff will be entered into the Utah/DCC REDCap AE database.

As described above, every 6 months in alignment with the DSMB meeting schedule, the study sites will provide a summary of SAEs to the DCC.

12.2 Definition and Reporting of Unanticipated Problems

12.2.1 Definition of Unanticipated Problems

This study protocol uses the following definition of Unanticipated Problems (UPs) to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected;
- Related or possibly related to participation in the research; and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

"Unexpected" means the nature, severity, or frequency is not consistent with either (a) the study procedures or study interventions that are described in section 2; and (b) the characteristics of the participant population being studied.

"Related" means there is clear evidence that the unanticipated problems were caused by the study procedures or study interventions involved in the research and "possibly related" means a reasonable possibility that the unanticipated problem(s) may have been caused by the study procedures or study interventions involved in the research.

12.2.2 Reporting of Unanticipated Problems

The study site investigator will report UPs to the lead principal investigator (PI). The lead PI will report UPs to the IRB of record. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, and/or outcome

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the timeline specified in the written reliance agreement between the IRB of record and the relying IRB at each study site.

13 STUDY OVERSIGHT

Study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) comprised of members with expertise in appropriate clinical, statistical, scientific, ethical disciplines.

The DSMB will meet before study enrollment begins and every six months thereafter, until the end of the study; to approve the study protocol prior to implementation; assess safety and effectiveness data; to monitor accrual of study participants; to study progress, and data integrity for the study. If safety concerns arise, ad-hoc meetings and more frequent standing meetings may be held.

The DSMB will operate under the rules of a charter that will be approved at the initial DSMB organizational meeting. At that time, data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the funding agency, the National Institute on Aging, regarding proceeding with the study as planned, proceeding with modifications, or terminating the study, as noted in the DSMB Charter.

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

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

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

13.1 Halting Rules

The DCC will monitor the safety data submitted by the study site investigator. The DCC will notify the DSMB chair when any SAEs deemed to be unexpected and related to study procedures or study interventions occur during the study.

In such an instance, the DSMB chair will provide recommendations regarding the temporary suspension of enrollment and/or administration of study procedures or study interventions. If warranted, an ad-hoc DSMB meeting will be convened.

14 STUDY MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Clinical site monitoring and remote monitoring for this study will be performed by the Duke/Vanderbilt (Clinical Coordinating Center or CCC) and Utah (Data Coordinating Center or DCC) Trial Innovation Centers, respectively.

14.1 Clinical Site Monitoring

The CCC utilizes risk-based methodology to identify and correct problems that may arise at sites. Details of clinical site monitoring will be documented in a supplemental study-specific risk-based Clinical Monitoring Plan (CMP), separate from this protocol. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports.

Site monitoring will be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim monitoring will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring for this protocol will consist of site initiation (prior to patient enrollment), interim monitoring, and close out. The site initiation may take place as group training made up of site investigators and research assistants.

Study monitors will evaluate study processes and documentation based on the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP). Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, NIH, and NIH Program staff. The NIH reserves the right to conduct independent clinical site monitoring as necessary.

The CCC may conduct clinical site monitoring remotely. Remote monitoring involves detailed review of the data entered by the clinical sites (KPGA, KPNW, KPGA and Essentia) and consultations with the clinical site investigators and/or research coordinator/manager to review safety and data quality. This may require uploading patient study files, regulatory documentation, or other source documents for the monitor to review. Alternatively, other methods, such as remotely viewing source documentation, may be utilized. This helps assure protocol compliance and accurate data collection. The CCC may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Plan (DSMP).

15 STATISTICAL CONSIDERATIONS

This section provides an overview of the planned statistical analyses for the RESOLVE study. See the RESOLVE Statistical Analysis Plan (SAP) for specific details related to the study hypotheses and analytic approaches.

15.1 Sample Size Determination

For the primary study outcome, clinically meaningful improvement (MCID; 30% reduction in overall BPI-SF score) in pain severity at 3 months, sample size requirements were calculated for a two-sided comparison of independent proportions with 90% power using Fisher's Least Significant difference method to account for three-way comparisons (specifically conduct Omnibus Wald Test for any difference between three groups and then conduct pairwise comparisons given an overall difference is statistically significant at the 0.05 alpha level). Sample size calculations assumed a usual care outcome rate of 15% who achieve the MCID of 30% reduction in pain severity from baseline to 3 months. The 15% usual care rate was chosen because this rate was observed among participants in the usual care arm of the study PI's recently completed PPACT trial[71] and it is similar to rates observed by others in the usual care arm of similar trials.[85] The necessary sample size of 1,863 (621 per arm) was calculated to detect a difference of 7.5% between a given intervention group relative to usual care in the proportion of individuals who attain a clinically meaningful change (30% reduction from baseline) in pain severity. A retention rate of 80% is estimated. Thus, to achieve this final sample size, at least 2,331 individuals will be randomized, 777 per intervention arm. A 7.5% detectable difference corresponds to 22.5% (relative change of 150%) of individuals in an intervention arm attaining a clinically meaningful change in pain severity.

Power for secondary analyses related to aim 1b (subgroup analyses) was also estimated. Sample size requirements for these secondary analyses were calculated using the same assumptions described above (i.e., a two-sided comparison of independent proportions using Fisher's Least Significant difference approach to account for three-way comparisons, with sample size calculations assuming an improvement rate of 15% in the usual care arm). The subgroup sample size was projected to range between 20% and 40% of the original 1,863 sample size since this should cover the range of the subgroup sample sizes of interest.

Power for Subgroup Analyses Ranging the Size of the Subgroup

Assumptions			**80% Power to Detect:**		
Subgroup Sample Size	**Usual Care (UC)**		**Intervention (Int)**	**Detectable Difference**	**Relative Change**
N (% of 1,863)	% UC		% Int	%Int - %UC	% Int / %UC
372 (20%)	15.0%		31.0%	16.0%	206.7%
558 (30%)	15.0%		27.7%	12.7%	184.7%
744 (40%)	15.0%		25.8%	10.8%	172.0%

There is 80% power to detect a 10.8% difference (relative change of 172%) between each intervention group and UC if subgroup sample size is 40% of the overall study population and 16.0% difference (relative change of 206.7%) if the subgroup sample size is 20% of the overall study population.

Note that in previous studies of this study team, sex, and comorbid mental health conditions (depression, anxiety) were not less than 40% of the population suggesting there is high power for the primary subgroups of interest. Further, the study is aiming to have at least 20% of rural/medically underserved residency and therefore there is good power for this subgroup. Individuals with negative social determinants of health comprise an exploratory subgroup since it is not clear how many people in this population a priori will have this indication.

15.2 Populations for Analyses

All analyses will be conducted following an intent-to-treat approach, including all individuals randomized regardless of their engagement with or exposure to the intervention.

15.3 General Approach to Statistical Analyses

All confidence intervals and p-values will be two-sided and statistical significance at the 0.05 level.

15.4 Baseline Descriptive Statistics

Descriptive statistics of the baseline study population by intervention arm will be provided, presenting percentages for categorical variables and means and standard deviations for continuous variables. The RESOLVE Statistical Analysis Plan (SAP) provides specifics on the planned analyses related to demographics and baseline characteristics.

15.5 Primary Effectiveness Analyses

Primary Outcome (Aim 1) Statistical Hypothesis: Both active interventions are expected to result in a higher proportion of patients achieving MCID (30% reduction in overall BPI-SF score) in pain severity relative to those receiving usual care at 3-month follow-up (primary time point).

Secondary Time Point Statistical Hypotheses: Both active interventions are expected to result in a higher proportion of patients achieving MCID (30% reduction in overall BPI-SF score) in pain severity relative to those receiving usual care at the 6 and 12-month follow-ups (secondary time points).

Modified Poisson regression[86,87] fit using generalized estimating equations (GEE) will be used to model the binary primary outcome, MCID in pain severity (30% reduction from baseline), 3 months (primary time point) and 6 and 12 months (secondary time points).

Interactions between each intervention and indicators of time (3, 6, 12 months) will be included to estimate time-specific intervention effects; the primary comparisons will be between the interventions and usual care at 3 months (i.e., primary effectiveness will test the size of the intervention coefficient at the 3-months timepoint). Adjustment will be made for baseline levels of pain severity, other stratification variables (sex, clinical site, and rural/medically underserved residency), and *a priori variables* predictive of outcome (multisite pain and co-occurring mental health condition).

The RESOLVE Statistical Analysis Plan (SAP) provides further information on the rationale for this approach as well as the specific details on the planned analyses.

15.6 Secondary Effectiveness Analyses

Secondary Outcomes (Aim1a) Primary Statistical Hypotheses: Those in both active intervention conditions will show greater improvements in overall pain severity, pain intensity (MCID and overall), pain-related interference (MCID and overall) and related quality of life outcomes (social role functioning, physical functioning, and patient global impression of change) relative to those receiving usual care at the 3-month follow-up.

Secondary Outcomes (Aim1a) Secondary Statistical Hypotheses: Those in both active intervention conditions will show greater improvements in overall pain severity, pain intensity (MCID and overall), pain-related interference (MCID and overall) and related quality of life outcomes (social role functioning, physical functioning, and patient global impression of change) relative to those receiving usual care at the 6- and 12-months follow-ups (secondary time points).

Analyses of secondary outcomes (Aim 1a) will follow the same proposed approach as Aim 1. Linear regression will be used to assess continuous outcomes and Poisson regression for binary and count outcomes. An interaction between intervention arms and time indicators will be included, and the primary time point for all secondary analyses will be 3 months following randomization; baseline levels of pain severity and all stratification variables will be included as covariates.

The RESOLVE Statistical Analysis Plan (SAP) provides details on these planned secondary outcome analyses.

15.7 Additional Effectiveness Analyses for Primary Outcome (Moderators and Mediators)

Moderator (Aim 1b) Statistical Hypotheses: For patients with more complex conditions (concomitant mood or anxiety disorders; multisite pain) or challenging social / environmental factors (rural/medically underserved or unmet social needs) the contact with a telephonic coach will result in better pain-severity outcomes when compared to those receiving online CBT-CP.

Moderator Analyses: Subgroup analyses will be conducted to determine the impact of the active interventions on specific populations and explore for potential heterogeneity of treatment effects by sex, age, race/ethnicity, rural/medically underserved residency, multiple pain conditions, mental health mood disorders, and negative social determinants of health. Analyses for Aim 1b will follow the same general approach as for Aim 1 but will be focused on assessing heterogeneity of treatment effects (sub-groups). Heterogeneous treatment effects by each potential moderator will be assessed separately. For each moderator, included in the regression models described in the analytic plan for Aim 1 will be a main effect for the moderator and an interaction between the moderator, intervention, and follow-up time, to estimate time-specific intervention effects within each subgroup defined by the potential moderator. The primary

comparison for Aim 1b will be of the interaction terms associated with each intervention arm at the 3-months follow-up time.

> **Mediator (Aim1c) Statistical Hypotheses**: Changes in pain catastrophizing, pain-related self-efficacy, and perceived support from baseline to 3 months will be mediators of treatment outcomes at 6 months for those in both active interventions.

Mediator Analyses: Mediation analyses will be used to assess and quantify the effect of theory-based mediators (pain-catastrophizing, pain self-efficacy, perceived support). Primary mediation analyses will assess the effect of the potential mediators on the primary outcome at 6 months, MCID in pain severity, while explanatory secondary analyses will investigate mediator impacts on secondary outcomes at 6 months.

The RESOLVE SAP provides further detail on the planned moderator and mediator analyses.

15.8 Economic Evaluation Analyses

For aim #2, a full economic evaluation of the CBT-CP interventions, compared to usual care, will be conducted, using the framework of cost-effectiveness, including the costs of implementation and maintenance, following best practice in economic evaluation.[88,89] This analysis will be conducted for the Kaiser Permanente clinical sites where the capture of all health care utilization is available through administrative data. Information on resources used to implement the intervention will come from the trial data collection instruments and from medical office staff, provider interviews, and study staff. All relevant resources used in the intervention delivery (e.g., training, counseling, fidelity assurance) will be included. EHR data will be used to identify and classify health care encounters and prescription medications. Using the framework of cost-effectiveness, the incremental cost per additional patient with a MCID in pain severity (30% reduction from baseline) will be estimated at 12 months, and the Quality-Adjusted Life Year (QALY) gained—utilities will be estimated using the EQ-5D-5L.[45]

Costs to be collected. Medical care utilization and intervention costs will be considered. Medical care utilization includes pharmacy, outpatient visits (including specialty care), inpatient stays, and referrals, and will be costed using standard costing algorithms[46,47] and Medicare fee schedules. In addition to total medical care costs, we will also undertake an analysis of pain-related care focused on utilization linked to pain conditions, identified by diagnostic and procedure codes, and pain-related medications. Intervention costs include program implementation (e.g., training, meetings, and supervision; patient identification, invitation, and screening) and delivery (e.g., online hosting, clinician calls). The analysis will take the perspective of the health plan (a principal decision maker for future implementation), so it will include all health system costs of intervention implementation and delivery in clinical settings.

Cost-effectiveness calculations**.** As done in prior economic evaluations of trials,[90] the cost-effectiveness of the intervention will be estimated using net benefit regression methods.[91,92] This technique uses a "net benefits" framework, comparing the incremental cost-effectiveness ratio to a range of potential values for a decision maker's willingness-to-pay (WTP) for a unit of health gain. A cost-effectiveness acceptability curve (CEAC) is constructed that illustrates the intervention's probability of being cost-effective at various levels of WTP for a unit of outcome (e.g., cost per QALY of $30,000 to $100,000). The regression framework allows ready evaluation of cost-effectiveness in subgroups (following the intervention's findings). Net benefit regression uses as the dependent variable, net benefit: $nb_i = \lambda \cdot effect_i - cost_i$ (from person-level

effect and cost data; λ = WTP level and is varied to construct the CEAC). Sensitivity analyses will be performed to assess the applicability of costs to other settings, the estimation of replication costs, and economies of scale.[93]

Health care cost comparisons: A comparison of the health care costs between the randomized groups will be conducted. These comparisons will include overall, and pain-specific costs. The table below describes the proposed categories of health care costs. Health care costs will be analyzed using generalized estimating equations with appropriate link functions.

Categories of Health Care Costs to be Assessed		
	Pain-related[1]	**Total**
Prescription medications		
Ambulatory encounters		
Primary Care		
Physical Therapy, Occupational Therapy and / or Physiatry[2]		
Pain Medicine/Pain Clinic		
Mental/Behavioral Health or Addiction Medicine		
ER or Urgent Care		
Other specialty medical care[3]		
In-patient hospital[4]		

1. Pain-related medications are identified by medication class (i.e., opioids, etc.). Pain-related in-person health care encounters are identified based on ICD-10-CM diagnostic codes.
2. Physical Therapy includes Physical Therapy, Occupational Therapy and Physiatry visits.
3. Specialty medical care includes in-person encounters with any non-primary care department that is not already included in the table.
4. Pain-related hospitalizations have a primary (or principal) pain-related ICD-10-CM diagnostic code.

15.9 Exploratory Effectiveness Analyses

The impact of the active interventions on exploratory outcomes will be assessed. These exploratory outcomes are described in detail in section 3.4 and include long-term opioid use, depression symptomology, anxiety symptomology, sleep disturbance, high impact chronic pain, and graded chronic pain. The same approach that is proposed for secondary outcomes and outlined above will be used.

15.10 Safety Analyses

Safety monitoring analyses will be prepared for the external Data Safety and Monitoring Board (DSMB) twice per year to align with the DSMB meeting schedule. See the Data and Safety Monitoring Plan for specific details on the data and safety monitoring procedures and reporting guidelines.

15.11 Planned Interim Analyses

There are no planned interim analyses of primary or secondary outcome data before the study is completed. However, if in context of evaluating the safety outcomes the DSMB requests interim effectiveness estimates they will be provided. No formal futility or effectiveness interim analyses will be conducted.

16 QUALITATIVE EVALUATION ANALYSES

The qualitative evaluation (Aim #3) will be guided by three frameworks. First is the EPIS implementation framework.[94] The EPIS framework emphasizes both the inner (organizational) and outer context (environmental context), which are both important to monitor. The outer context may pose unique issues in each implementation site and impact the intervention even when the inner context is stable and being implemented with a high level of fidelity and consistency.

The RE-AIM model[95,96] will be used to document and help triangulate and explain the research outcomes. This model has four components: Reach, Effectiveness, Adoption, Implementation, and Maintenance. Reach reflecting the percentage and characteristics of persons who receive or are affected by a program. The project will use EHR data to examine: 1) the percentage of patients excluded from the trial and the rationale for exclusion, and 2) the percentage of patients who participate in the program based on the denominator of all patients who were approached for participation in each health care system, as well as all potentially eligible patients in the health plan regardless of whether or not they were approached for participation. Effectiveness measures the impact of the intervention on primary and secondary outcomes. Further, the qualitative evaluation is critical for understanding the reach, recruitment, and effectiveness findings. Adoption is less relevant to the current study as the telehealth programs can and will be made available to patients completely outside the ambulatory care setting, thereby reducing or eliminating routine barriers for adoption of health care treatments. Implementation will be assessed by examining participant adherence to the two CBT-CP-based programs (data collected in an automated fashion from the painTRAINER platform and by the virtual CBT-CP coaches in that arm of the study). Finally, Maintenance, or the opportunity thereof, will be assessed through stakeholder interviews with clinical and operational leaders in each of the participating health care systems.

In addition to EPIS and RE-AIM, we will utilize the Theoretical Framework of Acceptability (TFA)[97] to explore in-depth issues of satisfaction. The TFA is a multifaceted construct that reflects the extent to which people delivering or receiving a health care intervention consider it to be appropriate. The TFA is complimentary to constructs in the other two frameworks, while further examining issues of acceptability, particularly for patients, less explored in either RE-AIM or EPIS. The TFA consists of eight primary domains that have temporal aspects (e.g., before, during, and after an intervention) and consider both anticipated reactions to an intervention as well as cognitive and emotional responses experienced with an intervention. The domains include affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. As with EPIS and RE-AIM, we will use the TFA to guide interview question development for all our stakeholders and will code for TFA related constructs (e.g., sense of burden to participate) in our analysis process.

All audio-recorded interviews will be professionally transcribed, and coding will be completed by trained coders using qualitative analysis software that aids management and interpretation of text-based and other non-quantitative data. Reliability will be addressed by creating coding definitions and modifying them as needed, clarifying coding instructions, and using an iterative process of coding the same text and comparing codes and discussing discrepancies. Analytic techniques best suited to answer the study aims, maximize validity, and develop an evolving understanding of study findings will be utilized. These techniques can include using queries to

produce reports of text associated with primary codes and synthesizing themes from this text. Retrieving coded information in multiple ways, including by participant features (e.g., gender, pain diagnoses) by a code alone, or by combinations of co-occurring codes. Searches for text strings that occur in the qualitative dataset will also be conducted. Analysis will involve comparing themes and responses across participants and within categories of participants to examine common patterns and differences in beliefs, attitudes, behaviors, and experiences. Additionally, to ensure validity, searches for areas of contradiction across participants[98-100] and across groups will be conducted. This approach to coding and data reduction will enable the examination of issues from a number of perspectives and ensures a thorough review of the data increase the breadth and depth of insights generate from the qualitative data gathered.

17 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

Sources of Materials

Data will be obtained from multiple sources: electronic health records and administrative health plan records; participant self-report (via online, mailed survey, or telephone administered surveys); audio recordings of participant interviews; audio/video-recordings of virtual intervention sessions; and utilization data from the painTRAINER website. Only approved research staff with a need to review or analyze data will have access to study assessment data, intervention program use data, aggregate EHR data or study transcripts. Only study staff involved with administering study-related assessments (survey or interviews for the qualitative evaluation activities), or study interventions will have access to individually identifiable private information about participants.

Electronic Health Record (EHR) and Administrative Data. Patient health care utilization and administrative data will be used for the identification of patients who are potentially eligible for the study and to examine pertinent health care utilization patterns among study participants (including health care encounters and pharmacy-related outcomes). All data will be extracted from EHR and administrative databases in each of the health care systems participating in the study. Prior to consent in order to identify potentially eligible patients, select variables will be extracted and uploaded into the study's electronic data capture system (EDC), which will be password-protected and accessible only to authorized study staff. Only the minimum variables needed to identify and recruit patients will be uploaded into the EDC. As part of the consenting process, participants will be informed that their EHR data will be linked to their assessment data and shared with the investigative team at KPWHRI to be included in analyses. No individual identifying data will be published or released, and data will be summarized and presented only in summary or statistical form.

Participant self-report data. Self-report data will be collected via online, mailed survey, or telephone-administered survey and entered into either the KP CHR REDCap or the University of Utah REDCap system, which will be password-protected and accessible only to authorized study staff.

Audio- and video-recordings. Audio-recordings related to subject interviews will be kept in password-protected electronic files on the servers maintained by KP. Audio- or video-recordings related to the delivery of the virtual CBT-CP intervention will be kept in password-protected electronic files maintained by KPWHRI and KP CHR on its servers. When relevant (for interviews), transcription will occur with participant identifiers removed. No individual-identifying data will be published or released, and data will be summarized and presented only in summary or statistical form.

Utilization data from the painTRAINER website. All data collected during participant interaction with the painTRAINER intervention will be done through a secure, password-protected, mobile-optimized website.

18 QUALITY CONTROL AND QUALITY ASSURANCE

The Clinical Monitoring Plan, maintained by the CCC, and Data Management Plan, maintained by the DCC, describe the processes related to quality management for the study.

Quality control (QC) procedures will be implemented beginning with the data collection and data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the study monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The study sites will provide access to all trial-related locations, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

19 ETHICS/PROTECTION OF HUMAN SUBJECTS

19.1 Ethical Standard

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

19.2 Institutional Review Board

The Vanderbilt University Medical Center (VUMC) IRB will serve as the single IRB (SIRB) for this study. The local IRBs for KPGA, KPNW, KPWA and Essentia will cede oversight to the VUMC IRB.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

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

Children under the age of 18 will be excluded. mHealth versions of CBT-CP have been developed for children and adolescents,[101,102] but they all include a family component that differs substantially from the telehealth CBT-CP programs under evaluation in this study, both of which were developed and tested among adult samples. Further, our standardized assessment measures were validated in adult samples and as such, are not always applicable to children and adolescents.

Adults who do not speak English will be excluded from study participation. The interventions to be studied in this comparative effectiveness trial have not been developed for or tested for effectiveness in non-English speaking populations and are therefore not available for inclusion in this trial.

19.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. This confidentiality is extended to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the study sponsor.

The study monitor(s) or other authorized representatives of the Data and Clinical Coordinating Centers (DCC & CCC), NIH and the Institutional Review Board (IRB), may inspect all study documents and records required to be maintained by the site investigators.

19.4.1 Certificate of Confidentiality

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

20 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and kept in a secure file container throughout the duration of the study. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

20.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Study staff are responsible for training interviewers and providing participants' clear and adequate instructions for survey completion so that valid data capture is accomplished.

Unanticipated problems and AEs identified must be reviewed by the investigator or designee.

Data will be stored at the University of Utah and KP CHR, which are responsible for security of their information systems.

20.2 Schedule and Content of Reports

The Data Coordinating Center will be responsible for creating the following reports or making the data available to the appropriate TIC/RIC: recruitment and data collection reports, ongoing QA monitoring and DSMB reports, and intervention monitoring reports. For safety analyses and DSMB report production, the JHU-Tufts Statistical Core, physically located at the Johns Hopkins University will examine or oversee data quality, create secondary variables, and perform exploratory data analyses (EDA).

20.3 Study Records Retention

Study records will be maintained for at least three years from the date that the last grant federal financial report (FFR) is submitted to the NIH.

Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses.

Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

20.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly as determined by the IRB.
These practices are consistent with ICH E6:

- Compliance with Protocol, section 4.5
- Quality Assurance and Quality Control, section 5.1
- Noncompliance, section 5.20

It is the responsibility of the Principal Investigator(s) to use continuous vigilance to identify and report any deviations within 7 calendar days of identification of the protocol deviation to the HEAL ERN within the DCC REDCap system. Protocol deviations that result in increased risk or affect the participant's rights, safety, or welfare will also be reported to the IRB and the NIA Program Official within 7 calendar days of identification of the problem.

21 PUBLICATION

The study PI in collaboration with select study team members will develop a publication policy which will specify publication procedures and authorship requirements. The study will comply with NIH's Public Access Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information, as described below.

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

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

22 DATA SHARING

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

The DCC will produce a public/releasable database from the RESOLVE study. The releasable database will be completely de-identified in accordance with the definitions provided in the Health Insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. Data elements that are considered unreliable will be deleted, and this will be noted in the documentation.

The policies for release of this database will be determined by the NIH. These policies are expected to focus primarily on the timing of data release. The preliminary plan is to release the database (defined below) at the time of publication of the primary manuscript, or within 12 months of last patient procedure, whichever comes first. Implementation of the plan will follow the HEAL Public Access and Data Sharing Policy as outlined at *https://heal.nih.gov/about/public-access-data*.

In accordance with policies of the NIH, the DCC will send the releasable database and its relevant documentation to the entity determined by the NIH or specific institute to be the repository for data created under the HEAL initiative.

Access to the releasable database housed in the NIH-assigned repository will be in accordance with procedures and regulations of the NIH or specific institute.

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