Transcending COVID-19 barriers to pain care in rural America: Pragmatic comparative effectiveness trial of evidence-based, on-demand, digital behavioral treatments for chronic pain

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Objectives, Sections 2.3.1, 2.3.2, 2.3.3, 3, 4.1, 4.2, 4.3, 5.1, 5.2 5.2, 5.5, 6.3, 7.2, 7.3, 8.1, 8.3, 9.2, 9.4.1, 9.4.3, 9.4.5, 10.1.1.2, 10.4.4	• Edits to verbiage in Objectives, SOA, and sections throughout • Added tablet under Criteria 5 for inclusion criteria • Revision to loss-to-follow-up definition • Added updates to potential risk/AEs sections • Edits to sample size, power estimation, and analysis • Edits to language regarding consent procedures and documentation • Updated contact info under key roles and study governances	Necessary edits

	• **Added Table 2 Validated codes and validation performance metrics for each COPC after references section**	
1.1, 1.3, 10.1.4	• **(Incorrectly modified description of VR study intervention to "one of three software programs;" implied painTRAINER is loaded on the headset)** • **Clarified study documents may also be shipped and honorarium may be sent to participants who do not need to return device** • **PROMI Anxiety Scale added to SOA** • **Additional instruments added to SOA** • **Reformatted Key roles and Governance table**	**Clarifying language leftover from pure VR studies**
1.3, 6.1	• **Added various self-reported querstionnaires to SOA** • **Updated description of EaseVRx intervention to reflect recent FDA authorization**	**Incorporated new questionnaires, FDA authorization of intervention**
1.1, 1.2, 1.3, 5.1, 5.5, 11	• **Updated amendment history for v3 and v4** • **Modified descriptions of intervention to clarify two different programs and methods of delivery** • **Updated schema to incorporate Week 12 survey** • **SoA updated to incorporate treatment usage and coping strategy questionnaires; cohort builders generalized** • **Inclusion criteria #1 clarified to indicate that chronic pain conditions are not explicitly limited to those listed in tables** • **Fourth recruitment site added (Bendcare)**	**General cleaning of protocol, incorporated new questionnaires, fourth recruiting site added**

	• **Supplentary ICD-10 code table created to capture additional qualifying conditions identified by study team**	
1.3	• **SOA modified and clarified**	**Additional surveys added, SSQ needed to be separated from Week 1**
5.5	• **Recruitment procedures modified to allow for recruitment of individuals with valid email that was not in the electronic medical record**	**These individuals should be eligible for enrollment.**
5.6, 8.3	• **New CRFs added about primary pain** • **Neck pain added as known risk**	**Primary complaint may differ from whichever one of many qualifying ICD-10 codes are found during chart review; neck pain added as risk**
5.5, 6.4	• **Recruitment procedures modified to allow for recruitment of individuals by phone or email with elimination of 7 day waiting period.** • **Compliance procedures modified to allow for student interns with restricted access to PHI to make calls relating to facilitate survey compliance and device returns.**	**Recruitment efforts to date suggest letters and waiting period are ineffective for this study population; all study teams agree that removing email requirements for contact improves access, equity, and diversity of potential study population.** **Some basic tasks involving brief interactions with patients to be delegated to student interns when possible.**
2.3.1, 10.1.8.1	• **Microsoft OneDrive added as possible secure cloud data management system**	**OneDrive has features favorable to study staff that Box cannot accommodate; several study processes**

5.5	• **Onboarding procedures modified to take into account new instructional videos** • **Compliance procedures clarified and modified to account for optional SMS text messaging via REDCap**	**Onboarding procedures now incorporate clear video instructions, and compliance monitoring updated to reflect current streamlined practices**
6.0	• **Exclusion criteria expanded to include history of seizure and prior exposure to either study intervention** • **Screener week failure criteria modified to exclude if any of 7 pain journals incomplete, housekeeping to reflect contents of finalized screener week surveys and procedures** • **Monitoring procedures expanded to allow for optional onboarding phone call, as instructional materials have for many patients rendered technical support calls obsolete. Patients may now use email confirmation to begin study procedures (see new study document "Study Onboarding Communications")** • **Survey expirations (active and screening) clarified and follow-up procedures modified to provide flexibility to study staff and statisticians** • **Defined expectation of survey missingness**	**Survey procedures modified following findings of 2022 monitoring visit by CS-IRB. Onboarding procedures streamlined to ease patient burden and adjust for changes to call screening for unknown numbers, which may cause participants to be unfairly withdrawn.**
5.5, 7.2	• **Included protocol for study staff to contact individuals who have not signed the ICF** • **Modified definition of replaceable participant to exclude individuals who used VR intervention before withdrawing from study**	**Contacting screened participants to possibly assist with eConsent can be used to improve sample diversity and enrollment.** **Study adequately powered based on withdrawals to date, and analyses should include individuals who found the intervention**

		unsatisfactory and subsequently withdrew
5.5	• **Compliance procedures modified to allow a participant's recruiting site study staff to contact via patient portal when allowed by their local IRB.**	**Study team is having difficulty contacting participants at non-CSMC from a California phone.**

Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
cLBP	Chronic Low Back Pain
CONSORT	Consolidated Standards of Reporting Trials
CBT	Cognitive Behavioral Therapy
CRF	Case Report Form
eCRF	Electronic Case Report Forms
EHR	Electronic Health Record
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ITQ	Immersive Tendency Questionnaire
LBP	Lower Back Pain
MRN	Medical Record Number
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
UP	Unanticipated Problem
US	United States
VR	Virtual Reality

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training. See Staff Training Log.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Cedars-Sinai Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form 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 to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

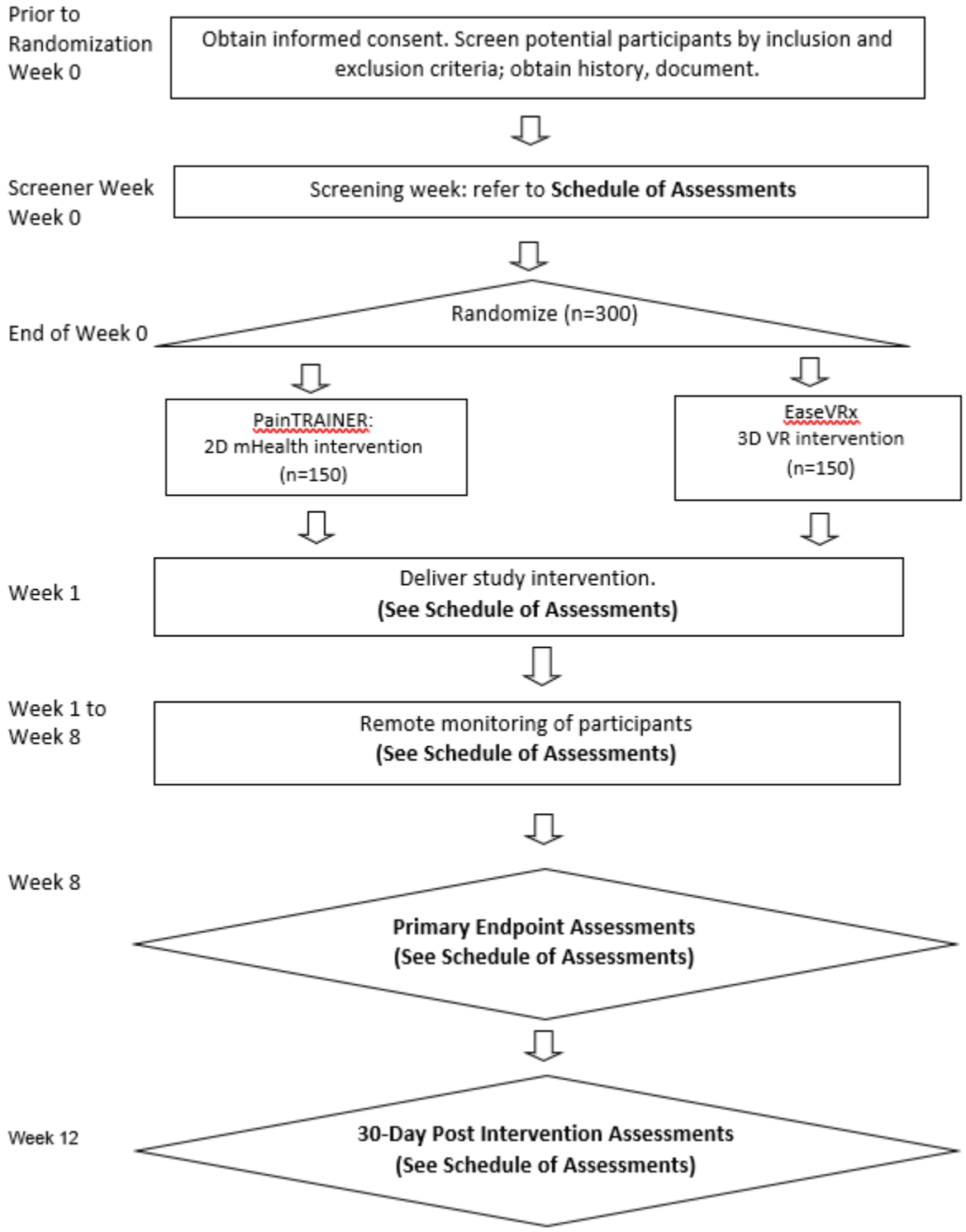
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Transcending COVID-19 barriers to pain care in rural America: Pragmatic comparative effectiveness trial of evidence-based, on-demand, digital behavioral treatments for chronic pain
Study Description:	This study will compare two available, evidence-based, digital pain treatment programs that patients can use at home. The goal is to see if one approach is better than the other, and whether certain patients respond to one more than the other. Study participants will be randomized to receive one of two treatment programs: Skills-Based VR or PainTRAINER. Study devices will be delivered to the participant's home with instructions for use via FedEx; participants will receive remote technical support. They will be followed for 8 weeks and complete Patient Reported Outcome (PRO) questionnaires to assess functional status, pain levels, and use of pain medications (including opioids). Participants will also be asked to provide consent/authorization to access medical records from their treating facility.
Objectives:	Primary Objective: To compare the effectiveness of EaseVRx and PainTRAINER in improving perceived pain intensity from baseline to 8 weeks.

	Secondary Objectives: To compare the effectiveness of EaseVRx and PainTRAINER in improving perceived pain catastrophizing over 8 weeks. To compare the effectiveness of EaseVRx and PainTRAINER in improving PROMIS anxiety over 8 weeks. To compare the effectiveness of EaseVRx and PainTRAINER in improving PROMIS pain interference over 8 weeks. To compare the effectiveness of EaseVRx and PainTRAINER in improving pain self-efficacy over 8 weeks. To compare the effectiveness of EaseVRx and PainTRAINER in reducing use of opioids over 8 weeks.
Endpoints:	Primary Endpoint: Daily Pain Intensity Secondary Endpoints: PROMIS Pain Interference, PROMIS Anxiety, Pain Catastrophizing, Pain Self-efficacy, and MME usage.
Study Population:	Individuals over age 13 with an ongoing pain problem that have experienced average pain intensity of >3 out of 10 within the previous 7 days.
Phase:	Phase 2
Description of Sites/Facilities Enrolling Participants:	Four outpatient clinic sites, including Cedars-Sinai Medical Center; Ochsner Medical Center; The University of Alabama at Birmingham; Bendcare Physician Network. In addition, participants may enroll remotely.
Description of Study Intervention:	All participants will randomly receive one of two interventions: a VR headset with a 3D Immersive VR therapy (EaseVRx) or a web-based 2D mHealth intervention therapy(PainTRAINER) -
Study Duration:	36 months
Participant Duration:	12 weeks

1.2 SCHEMA


Prior to Randomization Week 0
Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Screener Week Week 0
Screening week: refer to Schedule of Assessments
End of Week 0
Randomize (n=300)
PainTRAINER: 2D mHealth intervention (n=150)
EaseVRx 3D VR intervention (n=150)
Week 1
Deliver study intervention. (See Schedule of Assessments)
Week 1 to Week 8
Remote monitoring of participants (See Schedule of Assessments)
Week 8
Primary Endpoint Assessments (See Schedule of Assessments)
Week 12
30-Day Post Intervention Assessments (See Schedule of Assessments)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Baseline / Screening	Day 1 of Week 1	8-Week Intervention									Post Intervention
Week	**0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**12**
Prospective patients identified (Cohort Builderor Provider)	X											
Informed consent in person or over phone	X											
Verify eligibility in chart review or from Dr. Letter: • Medical history • Demographics	X											
Randomization	X											
Baseline Questionnaires (Listed below with)	X											
Shipment of VR device and/or study documents	X											
Technical onboarding call		X										
Milligram Morphine Equivalent (MME) Daily Dose	X									X		
Return of VR Device											X	
Deliver honorarium						X				X		X
Self-Reported Questionnaires												
NIH developed baseline demographics, biological sex	X (Day 1)											
Daily Pain Medications Used	X									X		
Daily Pain Intensity	X									X		
Pain Catastrophizing Scale	X (Day 4)		X	X	X	X	X	X	X	X		
PROMIS Anxiety Scale	X (Day 4)		X	X	X	X	X	X	X	X		
PROMIS Pain Interference Scale	X (Day 4)		X	X	X	X	X	X	X	X		
The Pain Self-Efficacy Questionnaire (PSEQ) 2-item short form	X (Day 4)		X	X	X	X	X	X	X	X		
Simulator Sickness Questionnaire (VR Only)		X										
Treatment Usage Questionairre			X	X	X	X	X	X	X	X		X
Events Assessment			X	X	X	X	X	X	X	X		
Custom Questions		X								X		
Treatment Expectation	X (Day 4)	X										
Concomitant Procedures Questionnaire	X (Day 4)									X		
Primary Pain Questionairre										X		
Coping with Weekly Pain Questionnaire	X (Day 7)									X		X

2 INTRODUCTION

2.1 STUDY RATIONALE

The COVID-19 pandemic has affected everyone in different ways. For people from rural areas of America with chronic diseases, particularly those who experience pain, the pandemic not only can worsen pain, but also it can trigger anxiety, depression, trouble sleeping, and substance use. This psychological distress is exacerbated by physical and social isolation, fear of seeking in-person visits, and diminished ability to access clinical care during the pandemic. One way doctors and health systems are reaching out is with video visits, where patients and their providers communicate online; however, video visits have limits. Therefore, we can help support them with other techniques. Beyond video visits, there are home-based programs that patients can self-administer to help manage their pain. These proven programs can overcome staffing shortfalls, be used across long distance to reach anyone in the world, and can be used at the time and place of the patients' choosing.

In this study, we will compare two available, evidence-based, digital treatment programs that patients can use at home. The goal is to see if one approach is better than the other, and whether certain patients respond to one more than the other. The first program is an app that can run on any smartphone or computer. The program offers an 8-week, at-home curriculum to learn and practice new skills that can help manage pain. The program runs on a standard screen on your phone or computer. The second program is also a proven, 8-week program, but it uses a technology called virtual reality, or VR. VR involves wearing specialized goggles that create a sensation of being in a 3D world. Evidence shows that virtual worlds can help people learn and retain new skills that help reduce pain.

The study will recruit 300 people from rural communities in California, Louisiana, Florida, and Alabama and randomize them into either the 2D or 3D programs. We will then follow patients for 8 weeks and measure their pain levels. We will also measure signs of distress, including anxiety, along with medications used for pain, such as opioids, and the impact of pain on overall quality of life. To conduct the study, we will ask patients to periodically complete short surveys online and give their permission for the research team to collect information from the electronic health record. We developed this study working with patient partners from the American Chronic Pain Association (ACPA), and they will be part of the research team throughout the conduct, analysis, and reporting of the study. The results will help patients, doctors, and health system decide which homebased, patient-administered, digital treatment programs for pain to choose, better enabling providers to select the right treatment for the right patient.

2.2 BACKGROUND

The COVID-19 Pandemic Presents Unique Biopsychosocial Barriers to Patients with Chronic Pain
More than 50 million Americans suffer from chronic pain,[1] defined as pain that persists for six months or longer.[2] In addition to experiencing the physical symptom of pain, patients with chronic pain endure a multi-dimensional illness affecting biopsychosocial health, including low energy, impaired cognitive functioning, disrupted sleep, and diminished physical health, mental health, and social functioning.[3-9] As a result, patients with chronic pain interact with the healthcare system frequently; one in five visits to a primary care provider is related to pain.[10]

The COVID-19 pandemic presents unique environmental, social, and physical barriers to patients with chronic pain. Data reveal that the global pandemic can worsen physical pain and trigger anxiety,

depression, insomnia, and substance use.[11-13] This psychological distress is exacerbated by physical and social isolation, fear of seeking in-person visits, and diminished ability to access clinical care.[11,13]

Although video telemedicine visits are vital to bridge physical gaps between patients and providers, they are insufficient to address the scale of pain-related medical needs and emotional distress created by the pandemic. Video visits and online support groups rely on the availability of a fixed and limited number of trained clinicians. This structural limitation cannot address the overwhelming impact of COVID-19 on mental health, including the 31% of Americans endorsing anxiety and depression during the pandemic, 13% who started or increased substance use, and 11% who seriously considered suicide during this period, according to U.S. Centers for Disease Control data.[14] In addition, telemedicine video visits can only occur at certain times of day and require that patients are willing to participate, are physically available and mentally prepared at the scheduled time, and reside in a home that affords sufficient privacy from others. Thus, additional treatment options are needed to bridge the growing gap between supply and demand of pain care services in the era of COVID-19.[11] This need is especially pressing for patients living in rural areas and the socially disadvantaged.

Evidence-based behavioral treatments for chronic pain are largely inaccessible to most Americans, particularly those in rural communities, due to limited availability of services coupled with COVID-19 restrictions on therapist-delivered treatments.[12] Moreover, barriers to pain care access, combined with exacerbated psychosocial distress caused by the pandemic itself, dually serve to amplify pain in this vulnerable patient population.[12] The CDC recognizes that the COVID-19 pandemic is triggering emotional distress in people with preexisting chronic diseases, a phenomenon labeled by some investigators as a "global storm of stress-related psychopathological symptoms."[15] The CDC established public-facing guidance to help citizens navigate troubling emotions,[16] and the Substance Abuse and Mental Health Services Administration (SAMHSA) launched a National Distress Helpline for people struggling to cope with pandemic stress.[17] Both the SAMHSA helpline and other mental health services around the country have experienced dramatic increases in calls for help.

In short, the COVID-19 pandemic has spawned a mental health crisis with disproportionate impacts on patients with chronic pain.[13,14,18] A national shortage in mental health clinicians existed before COVID-19. **Now, healthcare organizations must decide how to rapidly scale and deploy behavioral pain care to a geographically widespread and increasingly isolated populace; there is no time to wait for expansion of the mental health workforce**. There is an immediate need to deploy self-administered, remote, evidence-based treatments that leverage the time-tested science of cognitive behavioral therapy (CBT), long considered the gold-standard behavioral medicine for reducing pain-specific distress, anxiety, and depression in chronic pain.[19] Several meta-analyses demonstrate that fully-contained, self-administered CBT computer programs are feasible and effective for home-based management of chronic pain.[20-23] Moreover, these self-contained programs can overcome geographic, staffing, and timing barriers of traditional video and in-person visits, particularly in vulnerable rural communities. **For these reasons, an international COVID-19 consensus panel recently concluded that whenever possible, online self-management programs should be considered to help care for patients with pain during the pandemic.[24]** However, because traditional CBT typically requires 8-12 sessions with a trained provider, even in the limited places where CBT is available, attrition rates exceed 30% in clinical practice.[25] Poor access to CBT, particularly in underserved rural communities and now magnified by the COVID-19 pandemic, amplifies psychological distress and promotes the use of less effective but readily accessible modalities such as opioid medications.[12]

The COVID-19 Pandemic Differentially Impacts Pain Care in Rural Populations

The nearly 50 million Americans living in rural areas incur disproportionate risks from the COVID-19 pandemic.[26] Because rural Americans have higher rates of hypertension, heart disease, and obesity, endorse higher rates of cigarette smoking, have more disabilities, and are both older yet have less access to health insurance than non-rural Americans, rural Americans are at greater risk not only for developing adverse outcomes from COVID-19, but also face larger challenges in managing psychosocial consequences of the pandemic.[26] **As a result, rural communities are uniquely susceptible to the negative health impacts of COVID-19 and are considered highly vulnerable according to the CDC's Social Vulnerability Index (SVI).**

Telemedicine offers an important approach for delivering healthcare to remote and vulnerable populations with diminished access to healthcare, particularly for mental health services such as chronic pain management. Even before the pandemic emerged, data revealed rapid growth in mental health telemedicine use among rural Medicare beneficiaries[27] enabled by substantially increased access to the Internet, with roughly two-thirds of rural Americans now having access to broadband networks.[28] Although telemedicine has increased dramatically in the era of COVID-19,[27] there is still a marked shortfall in the availability of mental health and pain practitioners throughout the U.S, particularly in rural communities;[29] this mismatch in supply and demand differentially impacts vulnerable rural communities with diminished access to care.[27] **This vulnerability is further amplified by the disproportionate impact of the opioid epidemic on rural America,[30] now considered to be an "epidemic in the midst of a pandemic."[31]** Non-opioid pain care was a priority before the pandemic, but now it is even more pressing to strengthen delivery of pain-related mental health services, particularly in rural communities, as a consequence of the pandemic's unequal forces on rural vs. non-rural regions.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This study poses minimal risk to participants. Immediate risks may include minor psychological distress from questionnaire items asking about health and employment status. There is also a small[32] short-term risk of transient risk of VR-related "cybersickness" for those allocated to the VR arm of this study. Cybersickness is transient vertigo, nausea, or headache. It results from sensory mismatch between the visual and vestibular systems[33-36] and usually resolves within minutes of removing the VR headset. The prevalence of cybersickness has fallen with improvements in hardware and software. Technical advances have reduced eye strain, minimized physical discomfort of wearing a VR headset, and reduced unnecessary visual motion.[35] In the therapeutic setting, we also choose slow-moving scenes rather than highly kinetic visuals. As a result, cybersickness has become less prevalent and significant for people using VR.[35] In this study, each VR session lasts less than 20 minutes. Participants will be instructed to complete just one session during each use to reduce the risk of cybersickness. In very rare instances, materials used in VR headsets have caused a mild rash which resolves when the VR headset is discontinuedWe do not expect any meaningful risk associated with the 2D PainTRAINER program.

There are no anticipated long-term physical risks from participating in this study. There is a small risk of breach of confidentiality associated with the electronic collection and transmission of protected health information. This risk will be minimized by following proper procedures for assuring data integrity and confidentiality.

The following is our list of study participant confidentiality safeguards:

- ***Electronic files –*** data identifying participants will be stored in status tracking logs within password-protected excel files on Cedars-Sinai encrypted shared drives.
- ***Forms –*** survey forms and other pages containing personal identifying information will be saved within the REDCap system.
- ***Data listings -*** participant name, name code, hospital chart, record number, Social Security Number, or other unique identifiers will not be included in any published data listing.
- ***Data distribution*** - data listings containing PHI such as name, MRN, or other identifiers easily associated with a specific participant will not be distributed.
- ***Data disposal*** - computer listings that contain participant identifying information will be disposed of in accordance with institutional policies and procedures, after study completion.
- ***Access*** - participant records will not be accessible to persons/institutions outside those listed on the HIPAA form signed by -the participant.
- ***Storage -*** study forms and related documents retained during and after study completion will be stored within a secure Box and/or OneDrive folder accessible only by approved study staff. Some documents, such as survey exports, may be locally stored on a Cedars-Sinai encrypted shared drive or computer desktop during data analysis.
- ***Passwords*** – Multi-factor password authentication will be required to access documents stored on the cloud and on local desktops at Cedars-Sinai.
- ***User Training -*** study staff with access to clinical computer systems are trained and certified to maintain confidentiality prior to authorization by the Cedars-Sinai IRB.
- ***System Testing –*** new computer systems used by clinical staff are processed by the Cedars-Sinai IT (EIS) to ensure the password-activated systems perform as intended
- ***Certificate of Confidentiality*** – NIH funded research that involves human subjects and collects information which may identify a person is automatically protected by a Certificate of Confidentiality to prevent forced disclosures (e.g., subpoenas).
- ***Privacy Breach Reporting*** – In the rare instance where an accidental release of identifiable PHI may occur, it will be reported to the Cedars-Sinai IRB and the Cedars-Sinai Privacy Office for adjudication and corrective actions.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential immediate benefits include reduction of pain and general improvement in psychological health. Potential long-term benefits include improved functionality, reduced opioid use, and improvements in overall physical and psychological health. This research will contribute to societal knowledge about the safety and efficacy of therapeutic VR and will provide information about the use of digital health pain reduction programs in rural popluations.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Virtual reality hardware and software has advanced significantly in the last decade. Modern studies utilizing VR have found general satisfaction with devices among participants. The incidence and severity of VR-related side effects are low, and symptoms generally subside within minutes of taking off the headset. There is little discernable risk for PainTRAINER, as it is a program that will be accessed online from a computer or mobile device that the participant is already using. Still, some individuals may experience emotional and/or mental discomfort associated with learning ways to modify one's behavior and the decisions around whether and how to implement these strategies.

Participation in the study may alleviate pain among individuals who have previously relied on opioids, potentially enabling them to reduce opioid use and related side effects. Sustained pain relief also may allow individuals to return to work faster, improve physical mobility, and enhance biopsychosocial health. As a result, the short- and long-term anticipated benefits of participation outweigh the minimal short-term risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare the effectiveness of 3D immersive Skills-Based VR with 2D mobile health application in improving perceived pain intensity from baseline to week 8. The trial will be considered a success if there is statistical evidence of difference in improvement between EaseVRx group and PainTRAINER group.	The change from study baseline to week 8 in daily pain intensity as measured by the standard 11-point numeric rating scale (NRS) with a 24-hour recall is the primary endpoint. The minimally clinically important difference (MCID) on the pain NRS is 2 points.	The NRS response scale is most often recommended in guidance documents. The empirical basis slightly superior measurement properties (e.g., reliability, validity, responsiveness) across a wide variety of contexts compared to other response scales[37].
Secondary		
To compare the effectiveness of 3D immersive Skills-Based VR with 2D mobile health application in improving pain interference from baseline to Week 8. The trial will be considered a success if there is statistical evidence of difference in improvement between the EaseVRx group and PainTRAINER group.	The change from study baseline to week 8 pain interference as measured by the 8-item PROMIS PI scale is a secondary endpoint. This scale measures the consequences of pain on relevant aspects of life, including the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. We will test for a statistically significant difference of 5 points in the PROMIS PI score from baseline, and compare differences between either EaseVRx group and PainTRAINER group.	The PROMIS scale is a validated instrument with excellent content validity, construct validity, and reliability in patients with chronic pain.[38] Past work indicates that changes of 3.5 to 5.5 points in PROMIS-PI scores of people with LBP can be considered meaningful.[39]
To compare the effectiveness of 3D immersive Skills-Based VR with 2D mobile health application in improving pain self-efficacy from baseline to week 8. The trial will be considered a success if there is statistical evidence of	The change from study baseline to week 8 in pain self-efficacy as measured by the Pain Self-Efficacy Questionnaire (PSEQ-2) is a secondary endpoint. It is a two-item instrument designed to assess the extent to which people in pain believe they are presently	The PSEQ-2's validity and internal consistency were found to be sound and suitable for use in clinical and research settings. 2 items are preferable to 10 to reduce participant burden. Further its use has

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
difference in improvement between EaseVRx group and PainTRAINER group.	able to work and live a normal life despite pain (work includes housework and paid and unpaid work).	been widely used in studies of low-back and chronic pain[40].
To compare the effectiveness of 3D immersive Skills-Based VR with 2D mobile health application in improving PROMIS anxiety from baseline to Week 8. The trial will be considered a success if there is statistical evidence of difference in improvement between the EaseVRx group and PainTRAINER group.	The change from study baseline to Week 8 in anxiety as measured by PROMIS anxiety scale. We hypothesize residual pandemic-related anxiety can be captured by including this measure; increased anxiety at the population level is well borne-out in the literature. Improvement in this domain could support one intervention over the other for use during a pandemic or other similar event.	The PROMIS scale is a validated instrument with excellent content validity, construct validity, and reliability.[38] Past work indicates PROMIS-Anxiety scores among people with LBP is considered a responsive measure sensitive to meaningful changes.
To compare the effectiveness of 3D immersive Skills-Based VR with 2D mobile health application in improving perceived self-reported pain catastrophizing from baseline to Week 8. The trial will be considered a success if there is statistical evidence of difference in improvement between EaseVRx group and PainTRAINER group.	The change from study baseline to Week 8 in pain catastrophizing as measured by PCS SF-6 is a secondary endpoint. We will test for a difference in rates of high catastrophizing as defined by a score of ≥7 on the PCS-SF6, and compare these differences between EaseVRx group and PainTRAINER group.	The NIH Pain Consortium RTF draft standards for research on cLBP recommend a uniform minimal data set that includes self-report measures of pain catastrophizing.[44] Further, changes in catastrophizing are associated with improvement in multidisciplinary pain treatment.[45]
To compare the effectiveness of 3D immersive Skills-Based VR with 2D mobile health application in reducing use of opioids from baseline to Week 8. The trial will be considered a success if there is statistical evidence of difference in improvement between EaseVRx group and PainTRAINER group.	The change from study baseline to Week 8 in weekly average opioid dosage calculated as a 7-day average of daily maximum milligrams morphine equivalent (MME) is a secondary endpoint. We will test for a greater than .5 SD in change from baseline, and compare differences between EaseVRx group and PainTRAINER group.	Despite some evidence from randomized controlled trials (RCTs) on the efficacy of opioids in the short-term treatment of low back pain, little evidence is available on long term efficacy and safety. Lowering MME as prescribed while lowering pain is an important goal of cLBP treatments.[46]

4 STUDY DESIGN

4.1 OVERALL DESIGN

We will perform a two-arm RCT among a geographically diverse group of patients with mixed-etiology chronic pain. Using a random number generator, patients will be allocated in a 1:1 ratio at the site level between two self-administered, remotely deployed CBT delivery platforms: (1) a 2D mHealth app called PainTRAINER; and (2) 3D VR app called EaseVRx. The primary analysis will compare changes in pain intensity over 8 weeks upon completion of the standardized 8-week digital CBT protocols. Secondary outcomes will include pain catastrophizing, pain interference, self-efficacy, anxiety, and opioid use. Patient blinding is not possible in VR versus non-VR studies; we will explain the purpose of our study is to determine if one of two self-taught pain-management skills programs is more effective in helping manage pain, alongside current treatment. If so, how much more effective is it and which patients does the program help the most? Both programs have been proven effective; in other words, both programs have been studied and results for both showed improvement in patients' ability to manage their pain. To do this, participants will be randomly assigned to test either a virtual reality (VR) program called EaseVRx or an online/mobile program called painTRAINER. Because it is important for researchers to exhibit equipoise when describing the competing interventions, we will prepare a script that uses neutral language regarding the two interventions, as per previous VR research. In addition, data analysts will be blinded to patient allocation.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The two-arm study design will allow us to compare two available, evidence-based, digital treatment programs that patients can use at home. The goal is to see if one approach is better than the other, and whether certain patients respond to one more than the other. The 60-day study duration was chosen to because both EaseVRx and PainTRAINER programs are 8 weeks in duration.

4.3 JUSTIFICATION FOR DOSE

Prior research has shown that daily use of VR for 10 to 15 minutes is effective in managing pain, plus use as needed for breakthrough flares of pain. The skills-based VR therapy program, EaseVRx, is a standardized 56-day program consisting of scheduled daily virtual experiences. Each VR treatment experience lasts between 2-16 minutes, with an average duration of 6 minutes. To minimize the risk of cybersickness, participants are instructed to complete one VR treatment experience at a time. Given the low-risk nature of VR, they also may repeat experiences such as relaxation, breathing exercises, and games at other times during the day, in response to their pain.

PainTRAINER is among the most widely validated mHealth interventions for pain management.18-25 Originally developed by members of our team at Duke and Northwestern University with NIH funding, the app teaches evidence-based pain coping skills using a self-administered, home-based software program. The system delivers eight sessions via any web-connected platform, including Android or iOS smartphones, tablets, or personal computers. The digital curriculum covers progressive muscle relaxation, activity/rest cycling, pleasant activity scheduling, recognizing negative automatic thoughts, pleasant imagery/distraction, problem solving, and monitoring for maintenance. Patients complete one session per week in a pre-determined order. The program can be completed in a somewhat flexible manner to accommodate life and medical events but the 56 day programs must be completed within 66 days.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the online survey questionnaire that is emailed on Week 8, as shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as 66 days after the last participant is enrolled or when that participant completes the Week 8 survey questionnaire, whichever is sooner.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. have chronic pain, from any underlying condition, using as examples but not limited to the administrative definition of ICD-10 code series G89.X or one or more of 134 chronic overlapping pain condition codes, as previously standardized and validated by an expert panel (see Tables 2 and 3)
2. have experienced average pain intensity of >3 out of 10 within the previous week;
3. are >13 years of age;
4. are able to read/write English;
5. have either a personal computer, tablet, or smartphone;
6. live in a designated rural zip code as defined by the Federal Office of Rural Health Policy (FORHP) data (RUCA Codes 4-10).

5.2 EXCLUSION CRITERIA

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

1. have a condition that interferes with use of the intervention (e.g., significant visual or auditory impairment, any history of seizure);
2. are hospitalized;
3. are receiving active cancer treatment;
4. are receiving end-of-life care;
5. have cognitive impairment that affects participation.
6. have previously used the EaseVRx+ or painTRAINER programs

We will we will collect data on key patient characteristics, including type of pain condition, sex, age, race, ethnicity, State and zip code, Rural-Urban Commuting Area (RUCA) codes (a composite measure of population density, urbanization, and daily commuting), pain severity, opioid use, comorbidities, social support, and COVID-19 impacts (unemployment, financial hardship, family or personal COVID-19 diagnosis).

5.3 LIFESTYLE CONSIDERATIONS

Women who are currently pregnant or planning to become pregnant will not be excluded from the study

5.4 SCREEN FAILURES

All aspects of this study are conducted remotely, including the participants' use of the digital intervention at home and collection of all PROs via survey questionnaires administered electronically. In addition, the VR headset has independent value. To ascertain their willingness and ability to respond to survey questionnaires delivered by email, potential participants are required to respond to daily, electronic, one-item "Pain Journal" questions and complete other baseline survey questionnaires over the course of a "Screening Week," following informed consent but prior to randomization. A screen failure is defined as a participant who completes fewer than 7 daily "pain journal" surveys.

Participants are required to complete each survey within 14 days of the original send date, as these surveys will expire after 14 days. Age, socioeconomic status, race, and ethnicity are some of the information that will be collected for all participants even if they fail to complete any Screening Week surveys. Individuals who inform investigators during the Screening Week that they are no longer able or willing to participate in the study for any reason or who are discovered to meet any of the exclusion criteria will be recorded and withdrawn from consideration. Individuals who satisfactorily complete all 7 pain journals and baseline survey questionnaires contained therein will be enrolled and randomized.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target sample size is 300. The population impacted by this research broadly encompasses individuals with many different types of chronic pain conditions, including somatic, musculoskeletal, neuropathic, and visceral pain. Using data from the Federal Office of Rural Health Policy (FORHP), rural Louisiana has a high prevalence of nearly 32% non-Hispanic Black, rural California has 2.5%, and Alabama 22.7%. We will oversample with a target of 20% for non-Hispanic Blacks in this study. We will have a monitoring plan to ensure that we maintain our 20% goal throughout conduct of the study. Rural California is 30% Hispanic, while Alabama and Louisiana have fewer than 2% Hispanic rural populations. The mean across states is 11.2%. The national mean of rural Hispanic populations is 6.6%. Because we will likely receive more patients from Alabama and Louisiana than from California (because there are two sites in the Deep South vs. one in urban California), we anticipate a weighted mean of closer to 8% Hispanic and will therefore target this value for our study.

All four clinical sites have patient cohort search engines that will be used to identify patients with chronic pain. The informatics department at each site will pull zip code data for each potential participant, which will be matched with year 2010 RUCA zip codes provided by the USDA. This will provide a list of all possible participants that meet our desired criteria. We will monitor enrollment monthly and use the list to enrich enrollment as needed throughout the study to maintain the 20% target for the overall sample (across all three States).

Across the four recruitment sites (Cedars-Sinai, Ochsner, UAB, Bendcare) over 10,000 patients are designated as being in a rural area. Though all four sites are based in urban location. There is a significant amount of rural area surrounding each area. Note that Dr. Curtis from University of Alabama is associated with Bendcare and the UAB coordinator will serve the same role for patients identified from Bendcare.

Recruitment for the proposed trial will be maximized using several strategies:

- Patients will be screened over a period of 24 months. Due to the COVID-19 pandemic, remote recruitment, which we have implemented and proved to be effective in our previous VR trials, will supplement in-person recruitment to ensure that we can reach the target enrollment goal.

- Identification: The prospective participants will be identified through existing registries, provider recommendation, and via automated EHR review using queries / clinical trial search programs / cohort builders (e.g. Deep6, Slicer Dicer, i2b2) at partner sites.
- Recruitment: No in-person visits are required to be recruited for this trial.
    - Main Method: All eligible participants with a valid email in the medical record will be contacted by a research coordinator by email and patient-portal using an IRB approved recruitment letter to explain the study. An informational brochure will be attached to the email communication.
    - Alternative Method: If no valid email is available but a phone number is available, the study coordinator will contact the potential participant by phone to explain the study. At that time, the coordinator will also collect the potential participant's email (if available and the potential subject expresses interest in receiving additional information via email). An informational brochure will be attached to a future email communication.

      Justification for the alternate method: Our study was funded to address healthcare disparities for underserved and vulnerable populations (rural participants, in this case), and we are concerned that our study is excluding individuals who would otherwise qualify but have inadequate contact information on their chart, to the detriment of the study. For example, our inclusion criteria specifically target populations who are unlikely to be in close proximity to the participating academic health systems, and this condition naturally hinders opportunity to collect some/all personal information due to the infrequency of these (often all-day when travel time is included) visits. Especially with this specific study, the recruitment letter requirement may be biasing our study sample to reflect a population of higher tech literacy, closer proximity to the health center, etc. Further, we are underperforming the recruitment targets of Black and Hispanic individuals set by our NINR project officer, and all sites have patients from these cohorts without valid email addresses.
    - All patients will be able to opt-out of the study via email or by phone. We request removal of an official wait time between sending the email/letter and contacting subjects by phone. Our justification is that, to date, in the rural chronic pain study alone, 153 recruitment letters have been sent to Cedars-Sinai patients. However, none of them have contacted our study staff prior to the 7-day period, and of the 33 individuals who were sent a recruitment letter and later declined, only two declined by email. 98.7% of recruitment letters have not obviated the need for a follow-up recruitment call, and this response rate compares to our other trials. Most individuals do not recall seeing or reading the letter when finally reached by phone.
    - If contacting a patient by phone, study coordinators will ensure the identity of the person on the phone call is indeed the prospective participant that was intended to be called.
- Consent: An IRB-approved script will explain the purposes, procedures, and potential risks of the study and rights as research participants. REDCap will be used to email the IRB approved electronic consent form to the patient. Participants will have the opportunity to carefully review the electronic consent form and ask questions prior to signing. Study staff may reach out to participants who have been sent a consent form but have not yet signed to assist with the

eConsent process or record a reason for withdrawn interest, a slong as the participant has not indicated a reason for not signing the form. Participants will complete their consent forms electronically using the 21 CFR 11-compliant online REDCap platform. The informed consent will be signed by the patient and the designated investigator before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

- Post-Consent: A copy of the informed consent documents will be provided to the participants for their records via email, and via postal service if no email is available. Participants will consent remotely and those randomized to the VR arm will receive their study equipment through a secure FedEx package. Study participants will receive their study equipment or documentation through secure FedEx package delivery. Retention to the 12-week study will be managed using protocolized reminder calls, emails, and/or SMS text messages to complete the study surveys. . Study coordinators will contact the participant following non-completion of a survey if >1 week has elapsed since the initial survey send date. The study coordinator will employ a Tableau dashboard that provides protocol adherence data to guide contact decisions.
- Participants who complete the consent form will be required to finish the baseline questionnaires in order to be randomized and have the study equipment shipped to them as described above. Participants will be emailed tracking information and, if randomized into the VR arm, videos describing use of the intervention.
- Participantswill be called for study onboarding once the VR device or painTRAINER workbook is delivered to their home. During this call, patients will be asked if they reviewed the startup instructions that were provided in the intervention tracking information email, and coordinators will answer any remaining questions and guide participants through the device or program if necessary. If participants are unreachable by phone, study staff will seek to schedule a phone call or confirm the participant's understanding of study procedure by email, or by patient prior to initiation of study surveys. Contact information will be provided for technical support throughout the participant's study enrollment.

This protocol is not high risk for subject attrition; the intervention itself is considered low risk by our IRB.

Strategies for retention include the following:

- During the recruitment process, subjects will be educated about the importance of their role in contributing to research, to increase the likelihood that they will complete the patient reported outcome measures even if they stop using the intervention.
- Participants will be educated on how to use PainTRAINER or VR via educational videos, talking with study staff, and referring to any applicable documentation.
- The subject burden is low. Several data will be acquired passively, through patients using the PainTRAINER (2D mHealth intervention) or EaseVRx (3D VR intervention). There are no visits to their medical provider required by the research protocol.
- Subjects will be compensated for participation in this study (see budget).
- Retention to the 12-week study will be managed using three 24hr reminder emails, phone calls, or SMS text messages, as preferred by the patient, to complete PRO measures. Study coordinators will contact the participant following non-completion of a survey if >1 week has elapsed since the

initial survey send date. The study coordinator will have a dashboard that provides compliance information to the individual patient using a program called tableau (Mountain View, California).

- Participants may be contacted to facilitate study onboarding and survey compliance by their recruiting site study team via patient-portal when allowed by local IRB policy.
- Participants in the VR arm will be required to return the device after completing the surveys on the 8th week to be eligible for the honorarium.

As health services researchers working in highly diverse populations, we recognize that racial and ethnic minorities are underrepresented in clinical research for a wide range of important historical and cultural reasons. We also recognize that there are many strategies that can help overcome barriers and obstacles to participation in clinical trials. Considering the large target populations of Black and Hispanic populations in our rural populations, we will engage in several recruitment strategies designed to increase targeted recruitment, as follows:

- Clarify the agenda behind the research in all written and oral communications.
- Provide clear information about the clinical trial that avoids medical jargon.
- Make recruitment/retention a top priority for research staff.
- Provide regular feedback to referral sources about the status of trial recruitment.
- Speak informally to colleagues to promote protocol awareness and interest.
- Speak at professional and community meetings about trial protocols, and request referrals.
- Highlight our team members who are Black and Hispanic researchers.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The two active interventions evaluated in this study are EasVRx and PainTRAINER. EaseVRx is delivered via a commercially available VR headset. PainTRAINER consists of 2-D visualizations delivered via smartphone or computer.

Skills-Based VR: EaseVRx

EaseVRx was developed by AppliedVR in partnership with pain psychologist Beth Darnall, PhD, Associate Professor of Anesthesiology, Perioperative and Pain Medicine at Stanford University and an NIH- and PCORI-funded investigator in the use of VR for pain management. EaseVRx incorporates the evidence-based principles of CBT, mindful meditation, and physiologic biofeedback therapy using embedded biometric sensors. It combines psychoeducation, pain education, breathing training, relaxation exercises, and executive functioning games to provide a mind-body approach toward living better with chronic pain. The standardized, prescriptive, and reproducible 56-day program delivers a combination of skills training and CBT-related treatments through scheduled daily virtual experiences. The participants are allowed to complete as many sessions as they would like. In addition to the prescribed schedule of content the participant will have access to the full library of content. Each VR experience lasts between 2-16 minutes, with an average duration of 6 minutes. The VR treatment modules are designed to minimize triggers of emotional distress or cybersickness. There are 5 types of modules:

- **Interoceptive:** These modules are designed to help the user understand and perceive what is happening inside the body. They provide a biofeedback-like platform in which the changes in the observed environment reflect a progressively enhanced state of relaxation.
- **Education:** Help the user understand why the VR exercises are relevant to their pain, as well as teaching specific topics often used in pain psychology, including the neurobiology of pain, the role of mood and stress in pain, pain catastrophizing, activity pacing and setting goals. The goal is for the user to create self-management steps and a toolkit of strategies they can use to manage their response to pain.
- **360-degree videos:** High-quality 360 videos with voiceovers, music, and sound effects that are designed to maximize relaxation and engagement of users.
- **Game modules:** Games are designed to maximize distraction and engagement, increasing the cognitive load on patients, and decreasing their perception of pain.
- **Dynamic breathing:** These modules are based on evidence-based biofeedback training designed to enhance awareness of one's physiological response to pain and to self-regulate that response. In a virtual world, the user experiences a gamified biofeedback session in which they are introduced to awareness of their breath via visualization in the form of air bubbles. In multiple sessions, the user receives increasingly challenging tasks to practice diaphragmatic breathing while interacting with the virtual environment. The user is also asked to pace their breath according to an expanding and contracting ring in the environment to slow the breath and create physiological changes associated with relaxation. The user's exhale is measured by the microphone embedded in the headset, offering biodata-enabled immersive therapeutics.

The EaseVRx program has been authorized by the FDA to help with pain reduction in patients 18 years and older diagnosed with chronic lower back pain.

PainTRAINER (2D mHealth intervention)

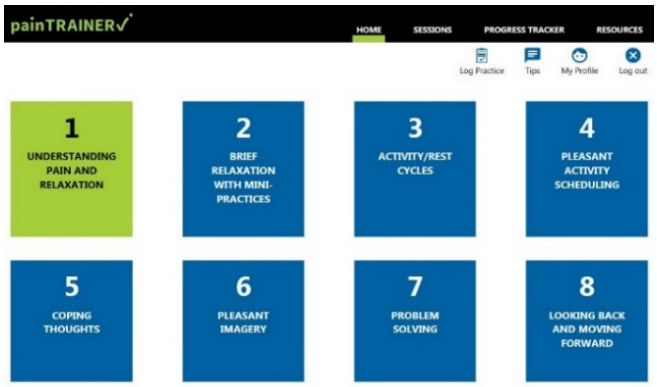
PainTRAINER is among the most widely-validated mHealth interventions for pain management.[47-54] Originally developed by members of our team at Duke and Northwestern University under NIH funding, the app teaches evidence-based pain coping skills using a self-administered, home-based software program. The system delivers eight sessions via any web-connected platform, including Android or iOS smartphones, tablets, or personal computers. The digital curriculum covers progressive muscle relaxation, activity/rest cycling, pleasant activity scheduling, recognizing negative automatic thoughts, pleasant imagery/distraction, problem solving, and monitoring for maintenance. Patients complete one session per week in a pre-determined order. The program can be completed in a flexible manner to accommodate life and medical events. For example, patients can close a session before completing it and later resume where they left off. Training is led by a computerized virtual coach and content is provided in audio to minimize reading and facilitate program completion for sick or low literacy patients. Important information is highlighted on screen with brief, large-font text, with photos, graphics, animations, and interactive exercises to reinforce learning.

PainTRAINER includes eight 35-45 minute sessions; each teaches an evidence-based pain coping skill. Users complete one session per week in a predetermined order and can close a session before completing it and later resume where they left off. They can also review completed sessions (e.g., an audio recording of a skill practice, or instructions on how to use a skill). **The program uses an adaptive, mobile responsive mHealth platform**: Users can access it with any Internet-enabled tablet, personal computer, or smartphone. **Smartphone access is important; these devices are increasingly the main platform used to access the Internet, including in underserved populations.** During development of *PainTRAINER*, patients clearly advocated for access to program content and resources through smartphones. Training is led by a

computerized virtual coach who speaks to users. **Content is provided in audio to minimize reading and facilitate program completion for sick or low literacy patients**. Important information is highlighted on screen with brief, large-font text, with photos, graphics, animations, and interactive exercises to reinforce learning. We also added other features to enhance learning and mastery of skills, guided by *social cognitive theory* (e.g., social modeling), *adult learning theory* (e.g., tying skills to personal goals and experiences), *principles of multimedia instruction* (interactive exercises, graphics to reinforce explanations), and *behavior change theory* (e.g., behavior tracking, reminders).

The program includes: (i) the Home Page (customized to users' progress and status by the expert system); (ii) Training Sessions; and (iii) the Expert System (a knowledge database and programmed decision rules or "algorithms" that customize users' experience based on their progress in the program). A login screen takes users to the home page where they access the current week's session, which is highlighted. From there, users access program sessions and features that allow them to manage reminders and goals, log practices, and review progress in easy-to-read graphs. **The interface applies accepted principles of user-centered design to enhance usability in diverse populations** (e.g., screen layout consistent with major websites; use of audio to minimize reading; simple menus placed predictably on-screen; clear and consistent navigation aids; direct access to important screens and help). **Screen elements are designed for a diverse population** (e.g., easy-to-read type, plain language and audio for low literacy users, images of people from diverse race/ethnic backgrounds). Written content follows federal guidelines for plain language to ensure it is easy to read, understand, and use. The program's back-end database tracks program use meta-data, including sessions experienced, time spent on session, and time of day the session was reviewed. These meta-data allow for secondary "dose-response" analyses. **Figure 1** shows the home page.

Figure 1: *PainTRAINER* home page



***PainTRAINER* has been validated in clinical trials, including multiple RCTs**. Bennell et al. studied the program in a participant-blinded trial of patients with chronic pain and found greater increases in function, pain coping, and global improvement than a control condition after eight weeks; benefits persisted at 52 weeks and 91% of participants (older adults, **largely from rural, low income areas, consistent with the current study population**) completed all 8 sessions.[47] Rini et al. found similar results in a controlled trial in patients with painful arthritis that demonstrated improved self-efficacy, reduced anxiety, and less pain-related interference with functioning.[48] Qualitative research reveals that patients find the program easy to use and are likely to recommend the app to others.[50] Taken together, research indicates that *PainTRAINER* as an effective and acceptable mHealth app that can reduce pain and psychological disability and has proven acceptable to users in rural communities. These findings are consistent with a Cochrane meta-analysis of RCTs of web-based behavioral interventions for persistent pain that found improvements in pain, impairment, depression, and anxiety.[55]

6.1.2 DOSING AND ADMINISTRATION

All participants are instructed to use the VR program at least once a day and as needed throughout the the 8 week study period. Thereafter, the participant can use the program as needed. Section 4.3 provides the justification of dose. PainTRAINER delivers eight sessions via any web-connected platform,

including Android or iOS smartphones, tablets, or personal computers. Patients will complete one session per week in a pre-determined order.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The PICO VR headsets loaded with the EaseVRx software programs will be provided by AppliedVR. The devices will be managed by the research team at Cedars-Sinai Medical Center.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

N/A

6.2.3 PRODUCT STORAGE AND STABILITY

The PICO VR headsets will remain in the boxes supplied by AppliedVR until they are shipped to participants.

6.2.4 PREPARATION

Prior to shipping a VR headset to a study participant, the headset battery will be checked to make sure it is fully charged. Any headsets that are handled by staff will be sanitized by cleaning the fabric surfaces using Virex, the plastic housing using Sani-Wipes, and the glass lenses using alcohol-based lens cleaner.

The group that gets the PainTRAINER program will be mailed a user's guide.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

We will allocate study participants using a random number generator to assign every-other patient to blocks of 2, 5, or 6 to ensure there is an equal distribution in the EaseVRx skills-based group and PainTRAINER group. Participants, their clinical providers, and study statisticians will be blinded to the study arm. The groups will be labeled as 1 or 0 at random. Datasets will be provided to the statistician using these group labels. A clinical research coordinator will ship VR headset containers to participants in the EaseVRx group and enter the label into the log of enrolled participants; the research coordinator who maintains the list of randomization assignments will not call participants on the telephone. Because the intervention is conducted in participants' homes and the data are collected remotely, the participants will not encounter each other and thus will be less likely to guess their study arm assignment. We anticipate there will be no circumstances during the study that require unblinding of an individual participant or a whole group because we do not expect any related SAEs to occur with this low risk intervention.

6.4 STUDY INTERVENTION COMPLIANCE

Data collection will be monitored daily by the study team. Participants will initially be sent automated reminder emails when they have not completed a survey questionnaire within a certain time frame after the original scheduled datetime. For the screener week and Week 8 daily pain journals, these reminders will occur 12 hours after and then 7 days after the original send datetime to best avoid overlapping

responses. For weekly surveys (SSQ+ to Week 8), automated reminder emails will be sent 48-hours after the original send datetime; if the participant does not respond to the first reminder, two additional 48-hr reminders will be sent. Study team members will call the participant after the third reminder if no or incomplete data are received. The articipant will be asked why they missed all three reminders and be encouraged to continue to complete surveys as they are sent. If the participant continues to miss subsequent surveys, they will be sent emails containing link(s) to active and incomplete surveys or considered lost to follow-up at the discretion of the study team.

Study participants are not expected to complete 100% of surveys sent to them during the course of the study; incomplete surveys are not considered non-compliance with the protocol. In addition, surveys may be completed out of temporal order and on the same day(s)—study statisticians will determine usability of these data.

Participants who are unable to complete >=80% of surveys sent during any of the three months of follow-up will be ineligible for the corresponding Amazon e-gift codes ($50 for month 1, $225 for month 2, and $25 for month 3, respectively.

Student interns with access only to the names and phone numbers of participants needing contact may place phone calls relating to survey compliance and return of equipment. Interns will **not** be performing activities related to recruitment or consent. If a subject has any questions outside of administrative issues, the call will be immediately transferred to a research coordinator or investigator.

6.5 CONCOMITANT THERAPY

Participants in the study can receive any ongoing treatment for their chronic pain.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

We do not anticipate any events that would cause the study intervention to be discontinued.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from the study at any time upon request. Participants who request to withdraw will be given the option to continue completing the periodic survey questionnaires, if they choose to continue responding to surveys, they will not be withdrawn. An investigator may withdraw a participant who develops any of the exclusions criteria in section 5. the

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who signed the informed consent form, were randomized and received the study intervention, and subsequently withdraw, or are withdrawn from the study without engaging with the study intervention (defined as any recorded VR or painTRAINER metadata by participant or self-reported usage of intervention in survey responses) will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to schedule an onboarding phone call within 30 days of device delivery or if he or she fails to complete the initial SSQ+ survey within 30 days of onboarding completion. For participants who complete the initial SSQ+ survey and fail to complete >80% of future surveys, and become unreachable by phone or email, the participant will be considered lost to follow-up 6 days following the email date of the participant's Day 60 survey.

If a participant fails to complete the weekly surveys within six days, the following actions will be taken:

- The research coordinator will attempt to contact the participant and counsel them on the importance of completing surveys and returning the equipment to be eligible for the gift card.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). Contact attempts will be documented in the participant's study record.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

We will capture all survey data via REDCap. REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies and operations. If subjects do not complete the surveys, they will be sent a reminder prompt.

Primary Outcome

The change from study baseline to Week 8 in monthly pain intensity as measured by the standard 11-point numeric rating scale (NRS) scale is the primary endpoint. Consistent with NIH Helping to End Addiction Long- Term (HEAL) guidance, we will measure daily pain with NRS for 7-days during baseline week 0, and again during the final week of the study (week 8). The minimally clinically importance difference (MCID) on the pain NRS is 2 points.

Secondary Outcomes

The change from study baseline to week 8 in pain interference as measured by the 8-item PROMIS PI scale is a secondary endpoint. The scale is rendered using a T-statistic, where a score of 50 represents the population mean and 10 points is a standard deviation (SD). Scoring of the instrument will occur in a SAS/R/STATA environment in which study statisticians are blinded to the study arm.

The change from baseline to Week 8 in pain catastrophizing as measured by the 4-item short pain catastrophizing scale is a secondary endpoint. The Pain Catastrophizing scale (PCS) short form measures rates of high catastrophizing as defined by a score of $\geqslant$7. Scoring of the instrument will occur in a SAS/R/STATA environment in which study statisticians are blinded to the study arm.

The change from study baseline to Week 8 in anxiety as measured by the PROMIS Anxiety Scale is a secondary endpoint. The scale is rendered using a T-statistic, where a score of 50 represents the

population mean and 10 points is a standard deviation (SD). Scoring of the instrument will occur in a SAS/R/STATA environment in which study statisticians are blinded to the study arm.

The change from study baseline to week 8 in pain interference as measured by the 8-item PROMIS Pain Interference scale is a secondary endpoint. The pain interference scale measures the consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The scale is rendered using a T-statistic, where a score of 50 represents the population mean, and 10 points is a standard deviation (SD).

The change from study baseline to week 8 in pain self-efficacy as measured by the two-item Pain Self-Efficacy Questionnaire (PSEQ-2) is a secondary endpoint. It is a two-item instrument designed to assess the extent to which people in pain believe they are presently able to work and live a normal life despite pain (work includes housework and paid and unpaid work). There is strong evidence for the validity and reliability of the PSEQ-2, its sensitivity to change, and suitability in clinical and research settings.

The change from baseline to Week 8 in 7-day average of daily maximum milligrams morphine equivalent (MME). Prescription opioid medication use will be collected via self-report and calculation of the 7-day average will occur in a SAS/R/STATA environment in which study statisticians are blinded to the study arm.

8.2 SAFETY AND OTHER PROCEDURES

Safety will be monitored by following up with participants for any adverse events (AE), assessment of adherence, monitoring of biometric information, and questionnaires by support staff.

8.2.1 PROCEDURES

Virtual Reality Headset data

Data from the PICO G2 4K device will be aggregated by AppliedVR's cloud-based software solution that implements robust industry standards to maintain secure databases and keep data private. The AppliedVR cloud server is a HIPAA compliant platform. The device account that corresponds with each device will be created using a clinical trial number that is only linked to the patient via our office list of patients enrolled in the study. AppliedVR does not collect personally identifiable information and does not collect IP addresses from synced participant devices in our database. Data will be stored and indexed in the AppliedVR server database whenever devices upload batches of analytic events, and the analytic events are timestamped. The data collected by the device will include time of use, date of use, and the module selected. Our database servers are IP firewalled and whitelisted such that they refuse any connection from IP addresses not preprogrammed by our team.

PAINTRAINER

PainTRAINER® metadata will be downloaded and provided monthly by the coordinator at Northwestern as CSV files containing timestamped records of content accessed at the individual device level. These records will feature a user-ID unique to each patient. A linking list containing study-IDs and user-IDs will be stored on a secure server behind the Cedars-Sinai firewall, and only associated with other study data following database lock. In order to monitor weekly adherence, study-staff will access a subset of the metadata limited to study-ID and timestamps of usage. These data will be subjected to QC procedures in a SAS/STATA/R environment.

Technical Support

Patients in both arms will receive remote technical support from the research team. The idea is that issuing technology is usually insufficient to achieve behavior change.

Patients will be provided with onboarding material as well as emails with a link to our lab's website. The website was developed based on experience from previous remote VR therapy clinical trial and feedback from patients within it. On the website we have instructional videos as well an extensive FAQ page.

REDCap survey data will also be monitored. We will assign two technical support staff members to monitor patients in both arms. Patients will receive a telephone number and email to contact support staff as needed.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Short-term AEs associated with the study include "cybersickness,"[32] a transient form of motion sickness that affects up to one in four people upon entering a VR environment. Cybersickness most commonly presents with a short-term feeling of dizziness that typically subsides quickly. There are no anticipated long-term AEs from participating in this study. A comprehensive list of all potential cybersickness symptoms can be found below:

- Nausea
- Fatigue
- Eyestrain
- Blurred vision
- Difficulty focusing
- Dizziness
- Vertigo (a sensation of spinning dizziness, as though the room or surrounding environment is spinning)
- Headache
- Fullness of the head
- Difficulty concentrating
- Postural instability

In very rare instances, materials used in VR headsets have caused a mild rash which resolves when the VR headset is discontinued. Participants may also experience neck pain if using the device. No AEs are expected with PainTRAINER.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be

considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. We do not expect any serious adverse events with the EaseVRx or PainTRAINER intervention.

8.3.3 CLASSIFICATION OF AN ADVERSE EVEN

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Research staff will call the patient if an event is noted in event assessment that is sent on a biweekly basis. Nothing more than mild to moderate side effects are expected.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Research staff will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during review of biweekly event assessments by a study team member as well as on

Day 1. We will employ a general question to allow the patient to provide an event description without bias by presupposing the nature of the event, as follows:

1) During the past 14 days, have you experienced anything uncomfortable, distressing or upsetting as a result of using the technology?
a. Yes
b. No
2) If Yes please describe what happened. A research staff member will follow-up up with you as soon as possible to learn more.
a. [open text]

A designated CRC will review the REDCap dashboard for completed AE assessments on a daily basis throughout the work week. Once they find a completed event assessment form, they will follow-up with a phone call. The following information be obtained from the patient during the call: onset of potential adverse event, event description, when they last used the technology, how long they used the headset, when they stopped using the headset, severity of the potential AE, outcome of the potential AE (see categories, below), time until resolution/stabilization of event, the perceived relationship of the event to the study intervention, whether or not the event was expected (Y/N), whether it was serious.

The outcome can be labeled using one of the following categories:
- Recovered, without treatment
- Recovered, with treatment
- Still Present, no treatment
- Still Present, being treated
- Residual effect(s) present-no treatment
- Residual effect(s) present-being treated

Research staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.3.5 ADVERSE EVENT REPORTING

Cedars-Sinai IRB
If a mild or moderate event occurs it does not need to be submitted to the Reportable New Information (RNI). If the event is an unexpected (not usually associated VR side effects) or severe event (requiring treatment), an AE will be submitted to the IRB as soon as possible but within at least 10 working days.

8.3.6 SERIOUS ADVERSE EVENTS REPORTING

SAE will be submitted to the Cedars-Sinai IRB via RNI as soon as possible by study coordinators, but no later than 10 business days from the Principal Investigator’s or study team’s awareness of the event, incident, information or outcome.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

Study coordinators will report unanticipated problems (UPs) to the Cedars-Sinai IRB as a RNI submission as soon as possible by study coordinators, but no later than 10 business days from the Principal Investigator's or study team's awareness of the event, incident, information or outcome. UPs include SAEs and AEs, which are both unexpected and possibly related to the research as well as SAEs and AEs that meet the definition of a Research-Related Subject Injury (RRSI) – a medical condition that is caused by and/or directly related to the research study (i.e., the condition would not have existed "but for" the subject's participation in the study), and requires diagnosis or treatment.

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, 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.

The following are actions that could be taken by the study staff:

1. No action
2. Revise protocol to eliminate apparent immediate hazards to subjects
3. Modification of inclusion or exclusion criteria to mitigate newly identified risks
4. Implementation of additional procedures for monitoring subjects 5 - Suspension of enrollment of new subjects
5. Notify currently enrolled subjects
6. Suspension of research procedures in currently enrolled subjects
7. Modification of consent documents to include a description of newly recognized risks (site and/or study wide)
8. Provision of additional information about newly recognized risks to previously enrolled subjects
9. Other, specify

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint(s):
Primary Outcome: Pain interference over time as measured by Daily pain intensity
Hypothesis: EaseVRx will lead to a greater improvement in 7-day average daily pain intensity than PainTRAINER between baseline and week 8.
Comparisons: EaseVRx vs. PainTRAINER .

Secondary Endpoint(s):
Secondary Outcome: Pain interference over time as measured by PROMIS-Pain Interference 8a (T-Scored, Continuous).

Hypothesis: EaseVRx will lead to a greater improvement in pain interference than PainTRAINER between baseline and Week 8.

Comparisons: EaseVRx vs. PainTRAINER .

Secondary Outcome: Pain catastrophizing over time as measured by Pain Catastrophizing scale (PCS) short form.

Hypothesis: EaseVRx will lead to a greater improvement in Pain catastrophizing than PainTRAINER between baseline and Week 8.

Comparisons: EaseVRx vs. PainTRAINER

Secondary Outcome: Anxiety over time as measured by PROMIS anxiety scale.

Hypothesis: EaseVRx will lead to a greater improvement in Coronavirus Anxiety Scale than PainTRAINER between baseline and Week 8.

Comparisons: EaseVRx vs. PainTRAINER

Secondary Outcome: Pain Self-efficacy Questionaire

Hypothesis: EaseVRx will lead to a greater improvement in Pain Self-Efficacy than PainTRAINER between baseline and Week 8.

Comparisons: EaseVRx vs. PainTRAINER

Secondary Outcome: Comparing the change from study baseline to Week 8 in weekly MME of prescribed medication between baseline and Week 8.

Hypothesis: EaseVRx will have a statistically significant decrease in opioid use in comparison to PainTRAINER between baseline and Week 8.

Comparisons: EaseVRx vs. PainTRAINER

9.2 SAMPLE SIZE DETERMINATION

Sample Size calculations and Power Estimation

Sample Size calculations and Power Estimation

Sample Size Calculation: The primary goal of the study is to test the effectiveness of *PainTRAINER* vs. *EaseVRx*, in reducing pain intensity. The trial will be testing if there is statistical evidence that either *PainTRAINER* or *EaseVRx* is more effective in lowering average weekly pain intensity after 8 weeks from start of intervention. We estimate power to assess the effect of the interventions on the treatment response (achievement of a minimally clinically important difference [MCID] of 2.0 on the NRS [56,57] (y/n)) using logistic regression, accounting for possible confounding factors for the primary outcome described in Aim 1. The dependent variable is the treatment response and the main independent variable of interest is *PainTRAINER* vs. *EaseVRx*. **Table 1** displays the minimum odds ratio that can be detected with 90% power with the two-sided 0.05 level of significance as a function of baseline probability of positive response when a patient is treated with *EaseVRx* and R^2, the proportion of variability in the predictor of interest that is explained by all relevant baseline covariates in the model using data from 150 patients in the *PainTRAINER* arm and 150 in the *EaseVRx*. For example, data from 300 patients achieve 90% power to detect an odds ratio of 2.25 if the probability of positive response when a patient is treated with *PainTRAINER* is 0.3 and 0.1 of the variability in intervention is explained by all other baseline covariates in the model. These odds ratios vary between 2.15 and 2.91 and are clinically meaningful. Therefore, we have enough power to test statistical significance of predictors in the multivariable logistic regression model. Regarding clinical significance, given an MCID of 2 points on the NRS and a SD of 2 on this scale from our own digital health trials, data from 150 patients in each group

Table 1. Minimum detectable odds ratio as a function of the proportion of variability in treatment type that is explained by all other relevant covariates in the model and the baseline probability of postitive treatment response.

Baseline probability	R^2			
	0.0	0.1	0.2	0.4
0.2	2.32	2.42	2.55	2.91
0.3	2.17	2.25	2.37	2.69
0.5	2.15	2.25	2.37	2.74

will achieve 90% power to detect a mean pain intensity score difference of 0.75, corresponding to a clinically meaningful effect size of 0.38 SD.

9.3 POPULATIONS FOR ANALYSES

All efficacy and safety data summaries and analyses will be performed by study arm using an Intent-to-Treat (ITT) population defined as all randomized patients. The number of patients identified as candidates for the study will be reported, as will the number consented. The number and percentage of patients randomized, patient population (ITT), and treatment status (completed, discontinued/withdrew) will be summarized both by treatment group and overall. Reasons for discontinuation/withdrawal will be presented. An exploratory, per protocol (PP) analysis will focus on patients who used the assigned intervention on at least 50% of days during the first 30-day period.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All statistical analyses will be performed jointly by the Cedars-Sinai Biostatistics Core and the Cedars-Sinai Center for Outcomes Research and Education (CS-CORE) using SAS® software version 9.3 or higher (SAS Institute, Cary, NC, USA), R version 3.5.0 or higher (R Foundation for Statistical Computing, Vienna, Austria) or Stata software version 14 or higher (StataCorp LLC, College Station, TX, USA). Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, minimum, median, and maximum as appropriate). Categorical variables will be summarized using the number and percentage of patients in each category. Data will be summarized with respect to patient demographic and baseline characteristics both across the study and by study-arm. The efficacy endpoints, safety assessments, and other outcome results for each treatment group will be summarized descriptively unless otherwise indicated. In addition, statistical model estimates of least squares means, treatment differences, p-values and 95% confidence intervals will also be provided where relevant. The fit of general linear models will be assessed using residual plots and/or other diagnostic plots as appropriate. The fit of logistic models will be assessed using Hosmer-Lemeshow goodness-of-fit and/or receiver operating characteristic (ROC) curves as appropriate. All statistical tests will be 2-sided and performed at the 0.05 level of significance unless stated otherwise.

Multiple Comparisons/Multiplicity: The family-wise type I error rate (FWER) for the statistical tests of the primary and secondary endpoints will be controlled at 0.05. To strongly control the FWER at this level, a gatekeeping approach will be utilized. A closed testing procedure will be employed to control the FWER. Any hypothesis tests conducted for model building purposes will be conducted outside of any gatekeeping.

Missing Data: We anticipate two sources of missing data: the failure of patients to complete assessments and loss of patients to follow-up. Data patterns of baseline covariates with missing values will be examined using the method of Little and in case the data is not missing completely at random, missing values will be imputed using fully conditional specification with the multivariate imputation by chained equations (MICE) algorithm under the missing at random (MAR) assumption. Fifty or so datasets will be generated and analyzed separately, and the results combined using the formula in Carmichael et al. Similar considerations will be applied to missing data on the dependent variable in a repeated measure mixed model by investigating patterns of missingness.

Sex as a Biological Variable: The effect of sex on each intervention will be assessed by fitting two separate multivariable mixed models for each of the study interventions. In each model, the dependent

variable is NRS pain intensity and the independent variable of interest is sex, after adjusting for all relevant baseline factors. The effect of sex will be tested at the 0.05 level of significance. To investigate the differential effect of sex on the study intervention, we will construct a multivariable mixed model for the PainTRAINER and EaseVRx interventions by including a treatment variable, sex, and the treatment x sex interaction term. The differential effect of sex is significant if the p-value of the test of interaction effect is less than 0.05.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Pain Intensity - The goal of this analysis is to test the effectiveness of PainTRAINER vs. EaseVRx in decreasing reported pain intensity. The trial will be a success if there is statistical evidence that either PainTRAINER or EaseVRx is more effective in reducing pain intensity. The primary outcome will be the baseline vs. week 8 difference-in-difference in 7-day average NRS pain intensity scores, dichotomized into if the MCID of 2 is achieved. The between arm difference of achieving the MCID of 2 will be tested using Chi-squared test.

- Additionally, we will use a logistic regression to determine whether the odds of achiving the MCID of 2 is different between the two groups after accounting for baseline-scores by including them as one of the predictors.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Pain Interference, Pain Catastrophizing, Coronavirus-Related Anxiety, and Self-Efficacy
The goal of these analyses is to test the difference in the effectiveness of PainTRAINER vs. EaseVRx in decreasing pain interference, pain catastrophizing, anxiety, and self-efficacy. While the concepts measured are different, and the tests of change distinct, the analysis approach will be similar for all PROs. Independently for each PRO, a two-sample t-test will be used to compare differences-in-differences between the arms. Additionally, we will use an analysis of covariance (ANCOVA) to determine whether the average gain is different between the two groups after controlling for baseline-scores by including them as covariates. If assumptions of ANCOVA are not met, we will consider generalized linear models, including ordered logistic regressions to determine whether the proportional odds of average gain in the scale are different between the two groups after controlling for baseline-scores by including them as covariates.

Opioid Usage - The goal of this analysis is to test the effectiveness of PainTRAINER vs. EaseVRx in decreasing weekly average milligrams morphine equivalent (MME) of prescribed medication between the baseline week and the week before week 8. Weekly average MME will be calculated as a 7-day average of daily maximum MME as prescribed. Analysis of this endpoint will proceed via ANCOVA, adjusting for subjects' baseline MME. We will assess the assumptions underpinning the ANCOVA model graphically and will undertake appropriate transformation of the weekly average MME outcome as deemed appropriate. If no suitable transformations can be found, bootstrapped confidence intervals for the between-group differences in weekly MME will be produced.
Both adjusted and unadjusted between-group comparisons will be presented with 95% confidence intervals.

9.4.4 SAFETY ANALYSES

All safety analyses will be descriptive. No statistical testing will be performed.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will summarize demographic and baseline characteristics both by treatment group and overall using mean and standard deviation or median and interquartile range for the continuous variables, and frequency and percentage for the categorical variables. Any time-to-event counts will be measured from the day of randomization. Body Mass Index (BMI) will be calculated according to: BMI=weight (kg)/(height (m))2. Age will be calculated according to: Age=(date of event-birth date+1)/365.25. Weekly average opioid dosage will be calculated as a 7-day average of daily maximum milligrams morphine equivalent (MME) as prescribed. Zip code will be matched to median income using census data as an aggregate measure of socio-economic status.

9.4.6 PLANNED INTERIM ANALYSES

No formal interim analysis or interim statistical testing for treatment comparisons is planned.

9.4.7 EXPLORATORY ANALYSIS

The purpose of Aim 2, as described in the application, is to detect heterogeneity of treatment effect (i.e. differential response to the same treatment due to individual traits) on pain intensity by PainTRAINER or EaseVRx. The results will enable the research team to work with patient partners to make recommendations for optimizing deployment of home-based digital behavioral treatment across a diverse populace. We will investigate the predictive value of key patient characteristics, including type of pain condition, sex, age, race, ethnicity, State and zip code, Rural- Urban Commuting Area (RUCA) codes (a composite measure of population density, urbanization, and daily commuting), pain severity, opioid use, comorbidities, social support, and COVID-19 impacts (unemployment, financial hardship, family or personal COVID-19 diagnosis). The analysis for each covariate will consist of an unadjusted test of interaction with treatment group in a multivariate logistic regression model with responder status (subject achieved MCID difference or did not) as the dependent variable. These models will include fixed categorical effects for treatment, covariate, and treatment-by-covariate interaction. Interaction terms with a significance level of less than .10 will be included in full model testing. The p-values of interaction terms will be presented, as will the odds ratios and 95% confidence intervals by treatment and covariate. If multiple interaction terms demonstrate a significance level of less than .10, we will use a least absolute shrinkage and selection operator (LASSO) approach to variable selection. We will also use multivariable logit modeling with receiver operator characteristic (ROC) curve analysis to measure the accuracy of the resulting model in predicting achievement of an MCID response as measured by the area under the ROC curve by c-statistic.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and electronic documentation of informed consent is required prior to starting screener week procedures.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Eligible participants will be identified by patient cohort search engines and providers at each clinical site and an IRB approved email explaining the study will be sent by a research coordinator from the site at which the patient was identified. All study staff at all sites will use the same approved scripts, emails, and other communication materials. These documents will be customized by site to indicate where or by whom the patient was seen, as indicated by "[ ]" in the IRB approved materials. The patient will be able to reply, within 7 days, to the eligibility letter with a request to opt-out of further study-related communication. A research coordinator from the recruitment site where the patient was identified will telephone those who do not opt out within 7 days to discuss their interest in study participation. An IRB-approved script will explain, in lay language, that this research study is being conducted jointly between Ochsner, UAB, and Cedars-Sinai and that Cedars-Sinai is the site that will be running the study. The script will also explain the purpose, procedures, and potential risks of the study and research rights of study participants. Study Coordinators will ensure the identity of the person on the phone call is indeed the intended patient. If the patient indicates interest in participating, the study coordinator will explain that the next and further communications will be from Cedars-Sinai in Los Angeles, CA, and that they should expect an email containing the informed consent documentation in the near future. Study staff at Cedars-Sinai will use REDCap to email the IRB approved electronic consent form to the patient. Participants will have the opportunity to carefully review the electronic consent form and ask questions prior to signing. Participants will complete their consent forms electronically using the 21 CFR 11-compliant online platform, REDCap. A child assent form will be included as part of the informed consent to allow for adolescent participants between the ages of 14 and 17 to be enrolled. Every subject will be informed of the approximate time to complete the consent process. A copy of the informed consent documents will be provided to participants for their records via email. The informed consent will be signed by the patient and the designated investigator before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected, and it will be emphasized that their medical care will not be adversely affected in any way if they decline to participate in this study.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the electronic consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to starting the screening week surveys. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

The informed consent states that any changes in pain management should be made with the participants treating physician.

10.1.1 STUDY DISCONTINUATION AND CLOSURE

We do not anticipate any events that would warrant study discontinuation and closure.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant privacy is strictly held in trust by the participating investigators, their staff, and their interventions. Therefore, 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 sponsor.

Representatives of the IRB or regulatory agencies may inspect all documents and records required to be maintained by the investigator for the participants in this study. The clinical study site will permit access to such records as needed.

Data in the study are collected in three ways: in real-time, at infrequent intervals throughout the study, and through medical record queries. Real-time data, including survey data delivered via mobile device, will be stored on secure servers hosted by CSMC secure servers and will contain only a unique identifier for each participant. Virtual reality adherence data will also be tracked in real-time and hosted on secure servers by AppliedVR; a separate unique ID will be assigned to each participant. Data collected at infrequent intervals throughout the study, such as entry, 14-day interval assessments, and exit questionnaires will be stored on secure CSMC servers with unique ID's for each participant. Data collected from medical record numbers will reside on secure CSMC servers and an ID will be assigned to each individual in order to abstract PHI/PII and the medical record number. Each dataset will utilize different unique ID's and a list linking each unique ID to each participant will be stored internally on the secured CSMC network. The linking list allows a researcher with access to the secured files to merge all data using statistical software, while maintaining data confidentiality.

To minimize risk of breaches in confidentiality associated with the access and recording of protected health information, study staff will be assigned unique passwords and usernames to access secure servers. Additionally, identifiable information for participants will be obfuscated using unique ID numbers and a linking list will be held in a secure location.

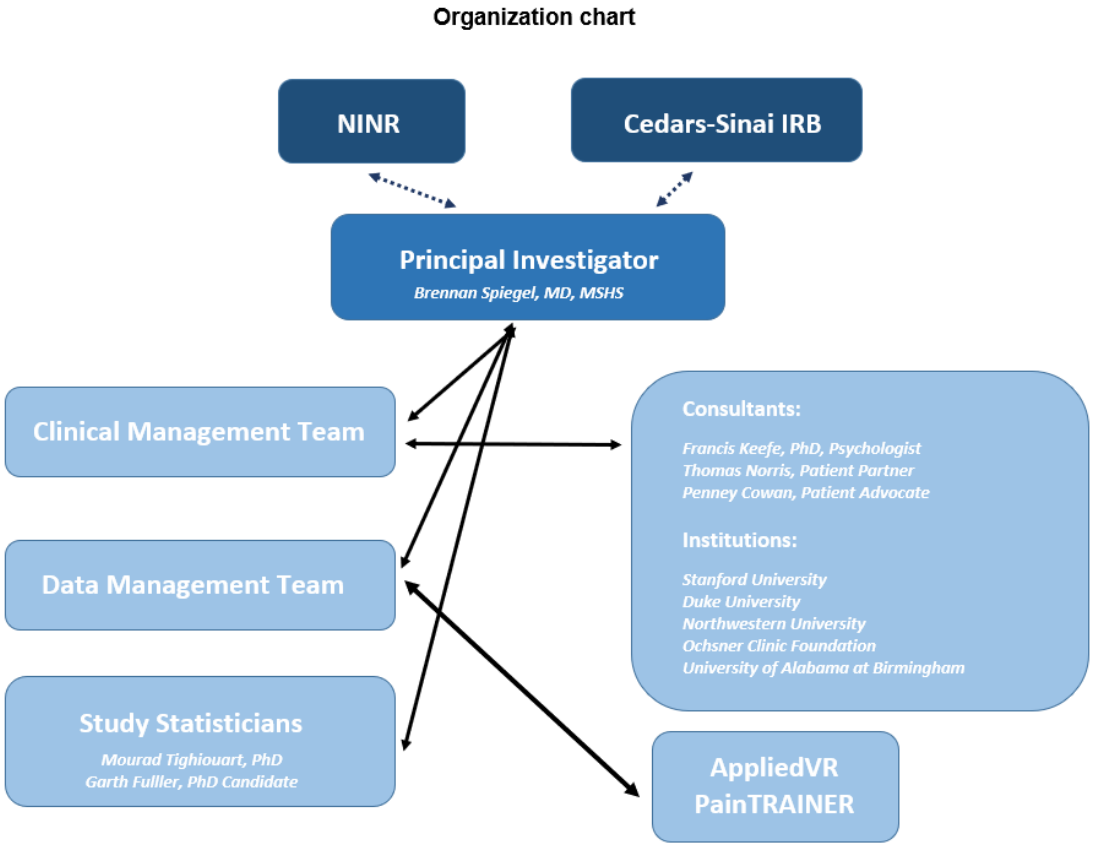
10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Role	Name	Contact Information
Principal Investigator	Brennan Spiegel, MD, MSHS Director of Health Services Research	Cedars-Sinai Medical Center 116 N. Robertson Blvd, Suite 800 Los Angeles, CA 90048 310.423.6784 Brennan.Spiegel@cshs.org
Co-Investigator	Yashar Eshraghi	Ochsner Clinic Foundation Napoleon Bldg., Suite 950 2820 Napoleon Ave. New Orleans, Louisiana 70115 (504) 842-5300 yashar.eshraghi@ochsner.org
Co-Investigator	Jeffrey Curtis, MD, MS, MPH Professor of Medicine	University of Alabama at Birmingham 510 20th Street South, FOT 802 Birmingham, AL 35294 205-975-2176 *jrcurtis@uabmc.edu*

As shown in Figure 1, below, the PI oversees the grant and interacts with all the key stakeholders, including NINR, the Cedars-Sinai IRB, and members of the Clinical Research Team, Data Management Team, and the Study Statisticians.



10.1.5 SAFETY OVERSIGHT

The study will be approved by the Institutional Review Board at the coordinating site (Cedars-Sinai) prior to starting any component of the trial.

This project will use the SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement (SMART IRB Agreement) to support single IRB review in compliance with NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. SMART IRB streamlines and advances collaboration by establishing a common IRB authorization agreement and standardizing the roles and responsibilities of all parties involved in the review and conduct of multisite research. Further, the SMART IRB Agreement outlines the responsibilities of all Participating Institutions, the Reviewing IRB, and Relying Institutions, in addition to detailing the communication plan between the Reviewing IRB and Relying Institutions.

Each engaged institution has joined SMART IRB by signing a Joinder Agreement to the master SMART IRB Agreement, thus avoiding the need for protracted negotiations about reliance details. Cedars-Sinai IRB has agreed to serve as Reviewing IRB, and the Relying Institutions (Ochsner and UAB), have agreed to cede review.

The sites have agreed that IRB review, regulatory oversight, and roles and responsibilities of the parties will be governed by the SMART IRB Agreement and the SMART IRB Standard Operating Procedures throughout the life of the project.

In joining SMART IRB, each site has designated a Point of Contact (POC) to provide the Reviewing IRB with knowledge about local context and facilitate coordination among the sites.

Given that this is a low risk study with centralized oversight by the reviewing IRB we do not believe that a separate Data Safety Monitoring Board (DSMB) will needed.

Personnel:

The Reviewing IRB at Cedars-Sinai will be composed of staff at Cedars-Sinai Medical Center with experience with randomized control trials in patients and expertise in pain management and patient reported outcomes.

In accordance with the SMART IRB Agreement and SOPs:

- Dr. Brennan Spiegel will serve as the Overall PI will serve as the primary contact on the Lead Study Team, and will distribute the results of IRB reviews and manage ongoing communications across site study teams.
- The POC for the Reviewing IRB will ensure appropriate communication with Relying Institution POCs.
- The POC at UAB will be Cassie Clinton.
- The POC at Ochsner will be Tracy Jones.

The Project Manager at Cedars-Sinai will be responsible for ensuring ongoing communication with all participating study teams via teleconferences and regular emails throughout the study. Key communication points will occur to:

- Disseminate IRB determinations and IRB-approved documents
- Educate study teams regarding the approved study and amendments to the study
- Alert study teams to problems that may affect the conduct of the study or the rights and welfare of research participants, such as unanticipated problems and serious noncompliance
- Inform study teams of any changes in study status (e.g., temporary suspensions of recruitment) or new information
- Facilitate submissions to the Reviewing IRB, including:
- Inclusion of site-specific requirements in consent documents
- Identification of any variability in study implementation across sites that must be communicated to the Reviewing IRB
- Collection of information from participating sites to include in continuing review reports to the Reviewing IRB
- Site-specific amendments
- Personnel updates (as required by the Reviewing IRB)
- Reportable events (e.g., noncompliance, unanticipated problems)
- Closure reports
- Ensure revisions to applicable conflict of interest management plans are provided to the Reviewing IRB

Purpose:

The primary goals of the reviewing IRB are as follows:

1. To monitor and advise on scientific and ethical issues related to the study implementation for the protection of human subjects

2. To review and approve the protocol and subsequently conduct annual reviews to determine whether participant safety has been adequately safeguarded

3. To review procedures and decisions regarding the adequate protection of specific participants when investigators break protocol because of adverse events or clinical deterioration

4. To review progress to see that enrollment goals have been met

5. To monitor and advise on ethical issues related to adverse events

6. To oversee the confidentiality of data, and quality of data collection, management, and analysis

7. To recommend, if necessary, discontinuation, modification, or termination of the study based upon emerging data (in the study and literature) and evaluation of risk/benefit ratio,

10.1.6 CLINICAL MONITORING

Schedule and Meetings:

The Reviewing IRB will be called upon whenever possible to render judgments in the advent of serious adverse event or clinical deterioration. The Reviewing IRB will meet once per year, or as needed. For each meeting, the Reviewing IRB will first meet in an open session attended by the principal investigator. The IRB will first review the research protocol and plans for data and safety monitoring. The IRB will review any problems in implementing the safety plan and for suggesting any necessary modifications to the safety plan. The reviewing IRB will then meet in a closed session for the purpose of reviewing emerging trial data at subsequent meetings.

1.4 Protection of Participants:

Confidentiality will be maintained by providing data without any identifying information to the committee.

2.1 Monitoring and Recommendations:

After the meeting, the Reviewing IRB will make recommendations to the PI. The Reviewing IRB will make recommendations concerning the continuation or conclusion of the study. The Reviewing IRB will monitor both safety and outcome data as part of the yearly review. No interim analysis is planned. Safety evaluations sent before the annual meeting will include review of adverse events for each participant. The Reviewing IRB will further consider external factors such as scientific and therapeutic developments that may impact the safety or the ethics of the study. The investigators will ensure that the Data and Safety Monitoring Plan is reviewed and approved by the reviewing IRB before the initiation of the study protocol.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Our quality assurance (QA) and control (QC) procedures are designed to support adherence to the protocol, obtain complete follow-up data for all participants enrolled, and establish and maintain high

standards for validity in collected data ahead of analysis. We approach QA as processes and safeguards for the prevention of data errors, and QC as mitigation efforts reducing impact from errors that have occurred during data capture and/or processing. While much of the QA effort occurs ahead of study launch, both efforts will require real-time and periodic tasks conducted through the duration of the study to ensure consistent checks of data integrity, completeness, and correctness.
QA via error prevention will focus largely on the REDCap system. Before data is entered into REDCap, study personnel will:

- Indicate units in question stems and use field validation whenever possible;
- Define and enforce range minimum/maximum where applicable;
- Ensure uniformity in date formatting across all REDCap date fields;
- Program pre-defined multiple-choice fields whenever possible (as opposed to free text);
- Indicate specific, standardized choices to identify data as intentionally missing (e.g “Not Applicable,” “Don’t Know”) as opposed to blank fields;
- Enforce skip/no-skip logic where appropriate;
- Standardize assignment of raw values. (i.e. if “Yes” is coded as a ‘1’ in one field, it should be coded as ‘1’ in all other project fields); and
- Use case and punctuation consistently across all field labels.

Each aspect of the REDCap data collection system will be tested before actual study data is collected. Study personnel will enter mock data into REDCap forms, serving as the “User” for acceptance testing. We will document the success or failure of a) the user interface for data entry, b) the on-line univariate and range data validation checks, and c) custom functions and coding. This mock data will be exported as SAS/R/STATA datasets by the research coordinator and subjected to QC procedures.
Our fundamental QC approach prioritizes error detection. Automated QC will occur in a SAS/R/STATA programming environment and will be tested/iterated on mock data before being employed monthly to exported datasets from both REDCap and the EHR. These QC programs will target potential data anomalies including:

- Missing data or forms;
- Out-of-range or erroneous data;
- Inconsistent, improperly formatted, or out-of-range dates; and
- Fields on a "completed form" not completed.

Once the study begins, routine QC reports will be prepared monthly by the study statisticians. These reports will describe target and actual enrollment, eligible participants screened with reasons for screen failure, and participant disposition (enrolled; active, completed, discontinued treatment, and lost to follow-up). These reports will also provide proportions of forms completed/missing, as well as summaries of problems identified by QC processes. Changes to QC programming will be documented and re-tested for accuracy.

Finally, daily monitoring for data completeness will be undertaken by the study team as a QA effort. Patients will initially be sent a reminder email when they have not submitted data after 2 days. If no response is given two additional 48-hr reminders will be sent. Research staff will attempt to contact the patient up to 3 times in one week.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study staff will develop, test, and maintain the data capture system using a web-based data collection system, REDCap, as the primary source of data entry and storage. Developed by Vanderbilt University, REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. The REDCap system provides a secure, web-based application that is flexible and provides: 1) an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry; 2) HIPAA compliant audit trails for tracking page views, data manipulation and export procedures; 3) record locking and electronic signature functions; 4) control over user rights to view and manipulate data; 5) a report builder capable of querying patient records; and 6) automated export procedures for SAS/R/STATA datasets.

The REDCap system complies with all applicable guidelines to ensure patient confidentiality, data integrity, and reliability. Quality assurance and control procedures will be applied to ensure the completeness, validity, and accuracy of the study database. The MOOP describes data collection processes, database development procedures, quality control processes, and reporting in greater detail.

EHR data will be retrieved by the Research Informatics and Scientific Computing Core (RISCC) at Cedars-Sinai, which facilitates interaction between the research community and the Epic data warehouse and production environment. We will collaborate with RISCC to design queries for portions of participants' records as defined in the data dictionary. The data extracts issuing from these queries will be delivered monthly as CSV files via Box and/or OneDrive, HIPAA-compliant cloud content management systems. These will then be converted to SAS/R/STATA data sets and subjected to QC procedures in a SAS/R/STATA environment.

VR device metadata will be provided monthly by AppliedVR as CSV files containing timestamped records of content accessed at the individual device level. These records will feature a device-ID unique to each patient. A linking list containing study-IDs and device-IDs will be stored on a secure server behind the Cedars-Sinai firewall, and only associated with other study data following database lock. In order to monitor weekly adherence, study-staff will access a subset of the metadata limited to study-ID and timestamps of usage. These data will be subjected to QC procedures in a SAS/R/STATA environment.

PainTRAINER metadata will be provided monthly by coordinator at Northwestern as CSV files containing timestamped records of content accessed at the individual device level. These records will feature a user-ID unique to each patient. A linking list containing study-IDs and user-IDs will be stored on a secure server behind the Cedars-Sinai firewall, and only associated with other study data following database lock. In order to monitor weekly adherence, study-staff will access a subset of the metadata limited to study-ID and timestamps of usage. These data will be subjected to QC procedures in a SAS/R/STATA environment.

10.1.8.2 STUDY RECORDS RETENTION

In compliance with Protection of Human Subjects regulations, records related to the conduct of this trial, including but not limited to source documentation, informed consent forms, essential study documentation, and documentation of IRB activities, will be retained by the Investigator for a period of 3 years following the official close of the study.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the reviewing IRB ASAP but within 5 business days of the Overall PI becoming aware of the deviation.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting the Cedars-Sinai Center for Outcomes Research and Education.

We will also comply with the data sharing policy at NIH under NOT-OD-08-033. We will submit the final manuscripts to the NIH National Library of Medicine PubMed central for archiving upon acceptance for publication.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. The Cedars-Sinai Identifying and Disclosing Researchers' Financial Interests in Research Policy: Human Research Protection Program requires the Principal Investigator and all members of the study team to disclose their, their spouses'/domestic partners', and dependent children's financial interests in the research regardless of the source of funding. Additional disclosure requirements may apply to investigators involved in Federally-funded research as described in the Cedars-Sinai Management of Industry Relations and Conflicts of Interest Program Policy: Corporate Integrity Program. The Cedars-Sinai Institutional Review Board (IRB) retains authority to determine if the research is allowed to proceed under the terms of the management plan developed by IR/COI considering the potential impact on the process and documentation of informed consent and the equitable selection of subjects. Review of disclosed COIs associated with a human research protocol by IR/COI is requested through submission of the CS-IRB COI Disclosure Form, which details IRB-supported guidelines on methods to manage, mitigate, or eliminate COIs.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2	10/4/2021	• Edits to verbiage in Objectives, SOA, and sections throughout • Added tablet under Criteria 5 for inclusion criteria • Revision to loss-to-follow-up definition • Added updates to potential risk/AEs sections • Edits to sample size, power estimation, and analysis • Edits to language regarding consent procedures and documentation • Updated contact info under key roles and study governances • Added Table 2 Validated codes and validation performance metrics for each COPC after references section	Necessary edits
3	11/15/2021	• (Incorrectly modified description of VR study intervention to "one of three software programs;" implied painTRAINER is loaded on the headset) • Clarified study documents may also be shipped and honorarium may be sent to participants who do not need to return device • PROMI Anxiety Scale added to SOA • Additional instruments added to SOA • Reformatted Key roles and Governance table	Clarifying language leftover from pure VR studies
4	1/10/2022	• Added various self-reported querstionnaires to SOA • Updated description of EaseVRx intervention to reflect recent FDA authorization	Incorporated new questionnaires and recruiting site

5	2/17/2022	• Updated amendment history for v3 and v4 • Modified descriptions of intervention to clarify two different programs and methods of delivery • Updated schema to incorporate Week 12 survey • SoA updated to incorporate treatment usage and coping strategy questionnaires • Inclusion criteria #1 clarified to indicate that chronic pain conditions are not explicitly limited to those listed in tables • Fourth recruitment site added (Bendcare) • Supplemtary ICD-10 code table created to capture additional qualifying conditions identified by study team	General cleaning of protocol, incorporated new questionnaires, fourth recruiting site added
5.1	3/4/2022	• Minor edits to SOA	Additional surveys added, SSQ needed to be separated from Week 1
5.3	4/5/2022	• Recruitment procedures modified to allow for recruitment of individuals with valid email that was not in the electronic medical record	• These individuals should be eligible for enrollment.
5.4	7/11/2022	• New CRFs added about primary pain • Neck pain added as known risk	• Primary complaint may differ from whichever one of many qualifying ICD-10 codes are found during chart review; neck pain added as risk
5.5	7/28/2022	• Recruitment procedures modified to allow for recruitment of individuals by phone or email with elimination of 7 day waiting period.	• Recruitment efforts to date suggest letters and waiting period are ineffective for this study population; all study teams agree that removing email

		• Compliance procedures modified to allow for student interns with restricted access to PHI to make calls relating to facilitate survey compliance and device returns.	requirements for contact improves access, equity, and diversity of potential study population. • Some basic tasks involving brief interactions with patients to be delegated to student interns when possible.
5.6	9/19/2022	• Microsoft OneDrive added as possible secure cloud data management system	• OneDrive has features favorable to study staff that Box cannot accommodate; several study processes
5.7	10/21/2022	• Onboarding procedures modified to take into account new instructional videos • Compliance procedures clarified and modified to account for optional SMS text messaging via REDCap	• Onboarding procedures now incorporate clear video instructions, and compliance monitoring updated to reflect current streamlined practices
6.0	3/28/2023	• **Exclusion criteria expanded to include history of seizure and prior exposure to either study intervention** • **Screener week failure criteria modified to exclude if any of 7 pain journals incomplete, housekeeping to reflect contents of finalized screener week surveys and procedures** • **Monitoring procedures expanded to allow for optional onboarding phone call, as instructional materials have for many patients rendered technical support calls obsolete. Patients may now use email confirmation to begin study procedures (see new study document "Study Onboarding Communications")** • **Survey expirations (active and screening) clarified and follow-up procedures modified to provide flexibility to study staff and statisticians**	• **Survey procedures modified following findings of 2022 monitoring visit by CS-IRB.** • **Onboarding procedures streamlined to ease patient burden and adjust for changes to call screening for unknown numbers, which may cause participants to be unfairly withdrawn.**

		Defined expectation of survey missingness	
6.1	8/21/23	• **Included protocol for study staff to contact individuals who have not signed the ICF** • **Modified definition of replaceable participant to exclude individuals who used VR intervention before withdrawing from study**	• **Contacting screened participants to possibly assist with eConsent can be used to improve sample diversity and enrollment.** • **Study adequately powered based on withdrawals to date, and analyses should include individuals who found the intervention unsatisfactory and subsequently withdrew**
6.2	10/17/23	**Compliance procedures modified to allow a participant's recruiting site study staff to contact via patient portal when allowed by their local IRB.**	**Study team is having difficulty contacting participants at non-CSMC from a California phone.**

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Table 2.
Validated codes, and validation performance metrics for each COPC.

COPC/Search terms	ICD-10 Code	N with code	N captured by search terms, %	True Positive, %	False Negative, %
Fibromyalgia	**M79.7**	8401	8263, 98.4%	19/20 95%	0/200%
• Fibromyalgia • fibrositis • fibromyalgia syndrome fibromyositis • FMS • diffuse myofascial pain syndrome					
Irritable Bowel Syndrome	**K58.0**	5551	5551, 100%	20/20 100%	0/110%
• irritable bowel syndrome • irritable bowel • irritable colon • IBS • mucous colitis • spastic colon • nervous colon	**K58.1**	1350	1350, 100%		
	K58.2	1459	1459, 100%		
	K58.8	239	239, 100%		
	K58.9	9828	9817, 99.9%		
Interstitial Cystitis/Bladder Pain Syndrome	**N30.10**	2111	2110, 99.9%	19/20 95%	0/10%
• interstitial cystitis • bladder pain syndrome • painful bladder syndrome • IC/BPS • IC/PBS • ("chronic pelvic pain" AND "urinary symptoms")	**N30.30**	23	23, 100%		
Chronic Prostatitis	**N41.1**	310	308.	19/20	0/2
• chronic prostatitis • inflammatory prostatitis • ("chronic" AND "prostatitis") OR ("prostatitis" AND "unspecified")			99.3%	95%	0%
Vulvodynia	**N94.810**	184	184, 100%	18/20, 90%	0/1, 0%
• Vulvodynia • Vestibulodynia • vulvar vestibulitis • vulvitis • vulvar discomfort	**N94.818**	1872	1871, 99.9%		
	N94.819	76	76, 100%		
Migraine	**G43.XXX** (exclude G43.6-[cerebral infarct] and G43.A- / [cyclical vomiting]	34604	34,567, 99.9%	20/20, 100%	0/20, 0%
• Migraine • Migraines • sick headache • chronic daily headache • status migrainosus					
Chronic tension-type headache	**G44.201**	168	168, 100%	20/20, 100%	1/20, 5%
• tension headache • tension type headache • stress headache • tension-vascular headache	**G44.209**	2873	2835, 98.6%		
	G44.211	42	42, 100%		
	G44.219	809	808, 99.9%		
	G44.221	447	446, 99.8%		
	G44.229	1274	1272, 99.8%		

COPC/Search terms	ICD-10 Code	N with code	N captured by search terms, %	True Positive, %	False Negative, %
Temporomandibular disorder	**M26.60**	1293	1265, 97.8%	18/20, 90%	9/20, 45%
• temporomandibular disorder • TMD • temporomandibular joint disorder • TMJD • temporomandibular joint disease • (("temporomandibular" AND ("disease" OR "disorder")) • TMJ syndrome • TMJ arthralgia • TMJ tenderness • TMJ pain • TMJ disease • TMJ dysfunction • temporomandibular joint syndrome	**M26.62**	1474	1462, 99.9%		
	M26.63	616	614, 99.7%		
	S03.0XXA	326	293, 89.8%		
Chronic low back pain	**M54.5**	43,850	33,169, 75.6%	19/20, 95%	8/20, 40%
• back pain chronic~6 • back pain persistent~6 • back pain recurrent~6 • back pain unspecified~6 • back pain nonspecific~6 • back pain idiopathic~6 • back pain functional~6	**M54.40, 41, 42**	10649	9470, 88.9%		
	M54.89	804	644, 80.1%		
Chronic fatigue syndrome • chronic fatigue • chronic fatigue syndrome • myalgic encephalomyelitis • CFS • ME/CFS • systemic exertion intolerance disease • SEID	**R53.82**	8917	8916, 99.9%	20/20, 100%	0/1, 0%
Endometriosis With pain	**N80.XXX AND**	1586	1561, 98.4%	18/20, 90%	6/20, 30%
• endometriosis pain~4 • endometriosis painful~4 • endometrioma pain~4 • endometrioma painful~4 • adenomyosis pain~4 • adenomyosis painful~4 • (("endometriosis" OR "endometrioma" OR "adenomyosis") AND ("pelvic pain" OR "dysmenorrhea" OR "dyspareunia" OR "intercourse pain"~4 OR "intercourse painful"~4))	**("R10.2" OR "N94.4" OR "N94.5" OR "N94.6" OR "N94.10 " OR "N94.11 " OR "N94.12 " OR "N94.19 ")**				

Table 3.

Additional codes identified by study team which capture chronic pain conditions.

ICD-10 Code	Description
M05.*	Rheumatology
M06.*	
M45.*	
M46.*	
L40.5*	
M1A.*	
M15.*	
M16.*	
M17.*	