Home-based virtual reality for chronic pain: protocol for an NIH-supported randomised-controlled trial

Brandon Birckhead, Sam Eberlein, Genie Alvarez, Rebecca Gale, Taylor Dupuy, Katherine Makaroff, Garth Fuller, Xiaoyu Liu, Kyung-Sang Yu, J T Black, Mariko Ishimori, Swamy Venuturupalli, Joseph Tu, Tom Norris, Mourad Tighiouart, Lindsey Ross, Karma McKelvey, Mark Vrahos, Itai Danovitch, Brennan Spiegel

ABSTRACT

Introduction Chronic pain is highly prevalent and associated with a large burden of illness; there is a pressing need for safe, home-based, non-pharmacological, interventions. Virtual reality (VR) is a digital therapeutic known to be effective for acute pain, but its role in chronic pain is not yet fully elucidated. Here we present a protocol for the National Institute of Health (NIH) Back Pain Consortium (BACPAC) VR trial that evaluates the effectiveness of three forms of VR for patients with chronic lower back pain (cLBP), a highly prevalent form of chronic pain.

Methods and analysis The NIH BACPAC VR trial will randomise 360 patients with cLBP into one of three arms, each administered through a head-mounted display: 1) skills-based VR, a program incorporating principles of cognitive behavioural therapy, mindful meditation and physiological biofeedback therapy using embedded biometric sensors; 2) distraction-based VR, a program using 360-degree immersive videos designed to distract users from pain; and 3) sham VR, a non-immersive program using two-dimensional videos within a VR headset. Research participants will be monitored for 12 weeks using a combination of patient-reported outcomes administered via REDCap (Research Electronic Data Capture), wearable sensor data collected via Fitbit Charge 4 and electronic health record data. The primary outcome will be the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference scale. Secondary outcomes will include PROMIS Anxiety, PROMIS Sleep Disturbance, opioid prescription data and Pain Catastrophizing Scale Short Form. A subgroup analysis will explore patient level predictors for VR efficacy.

Ethics and dissemination Ethics approval was obtained from the Institutional Review Board of Cedars-Sinai Health System in April 2020. The results will be disseminated in a peer-reviewed journal.

Trial registration number NCT04409353.

INTRODUCTION

More than 50 million Americans suffer from chronic pain, defined as pain that persists for 6 months or longer. Patients with chronic pain endure a multidimensional illness that in addition to physical symptoms of pain, affects biopsychosocial health, including low energy, impaired cognitive functioning, disrupted sleep, diminished physical and mental health and diminished social functioning. As a result, patients with chronic pain interact with the healthcare system frequently; 20% of primary care visits are related to pain.

Evidence-based behavioural treatments for chronic pain are largely inaccessible to most Americans, particularly those in rural communities, due to limited availability of services coupled with recent COVID-19 restrictions on therapist-delivered treatments. There is a need to remotely deploy self-administered, evidence-based treatments that leverage cognitive behavioural therapy (CBT), long...
Therapeutic virtual reality (VR) has emerged as a promising evidence-based treatment modality for reducing both acute and chronic pain.17–25 The ubiquity of high-performance computing has reduced both the size and cost of VR devices such that portable VR units are feasible for everyday in-home use. Most VR research has assessed pain only immediately after a VR experience.18 21–24 Further, most studies focus on mere distraction to impact the experience of pain (‘distraction-based VR’); a small minority of studies assess more complex VR modalities that teach extensible skills using CBT principles, guided meditation and biofeedback-based breathing exercises (‘skills-based VR’).

The primary objective of this study is to assess the efficacy immersive skills-based VR and distraction VR in decreasing pain interference compared with placebo VR among patients with chronic lower back pain (cLBP), a model chronic pain condition that is both common and costly.26 The secondary objectives focus on the efficacy of VR to improve pain interference, perceptions of sleep quality and anxiety, self-reported pain catastrophising and reduce use of opioids. Tertiary objectives include studying the impact of VR on patient reported outcomes (PRO) of depression and physical function, as well as biometric variables measured with a wearable sensor. In addition to assessing PRO and biometric data, the study also aims to identify patient-level predictors for VR efficacy. Here we present the protocol as a model for conducting research on using VR to manage chronic pain.

METHODS/DESIGN

Design

This prospective, three-armed randomised controlled trial will be conducted with participants within Cedars-Sinai Health System (CSHS), an academic medical centre based in Southern California. Two different VR pain reduction programmes will be compared with a control placebo VR program among patients with cLBP. Randomisation of all 360 subjects will be performed via Research Electronic Data Capture (REDCap) (Nashville, Tennessee), 1:1:1 across the three study groups, with random block sizes ranging from 3 to 12 subjects, stratified by site, using tables generated from Stata V.16.1 (College Station, Texas). Block randomisation is implemented in order to ensure that patients are equally assigned to each treatment group and varying the block size reduces selection bias by preventing predictability of the allocation of patients. The randomisation table was created by an independent biostatistician at CSHS. Each arm will include one-third of the total population randomised. Potential participants will be referred by physicians at the designated clinical sites or identified using the Deep 6 AI cohort building software (Pasadena, California), which uses natural language processing to search electronic health record (EHR) data for patients meeting study inclusion and exclusion criteria throughout the healthcare system. The sites of randomisation will include patient search engine recruitment (Deep 6), orthopaedic recruitment sites, rheumatology recruitment sites and pain clinic recruitment sites.

The study has been approved by the Cedars-Sinai Institutional Review Board (IRB) (STUDY00000631) and is funded by the National Institute of Health (NIH) Helping to End Addiction Long-term initiative as part of a group of studies within the NIH Back Pain Consortium (BACPAC) programme. The IRB-approved consent includes the data sharing plan provided by BACPAC. The study is registered at ClinicalTrials.gov. No post trial care is planned for this study.

Setting and sample

All aspects of this study will be conducted remotely, including the participants’ use of VR therapy and Fitbit (Mountain View, California) wearable motion and sleep tracking device. Collection of all patient reported data is performed electronically via REDCap, a secure web application. While REDCap can be used to collect a wide variety of data (including 21 Code of Federal Regulations Part 11, Federal Information Security Management Act and Health Insurance Portability and Accountability Act (HIPAA)-compliant environments), it is specifically designed to support online or offline data capture for research studies and operations.

All of the following eligibility criteria must be met: age >13, lower back pain that has persisted at least 3 months and has resulted in pain on at least half the days in the past 6 months, able to provide consent, willing to comply with all study procedures, comprehend spoken and written English, has access to either a compatible android or iOS smartphone or personal laptop or desktop computer (excluding tablets) to complete surveys and has access to email. Women who are currently pregnant or planning to become pregnant are eligible.

Patients will be excluded if they: (1) have a condition that interferes with VR usage including: history of seizure, facial injury precluding safe placement of headset, significant visual impairment that impacts ability to see the VR images or hearing impairment that impacts ability to follow audio instructions; (2) participated in a previous VR clinical study; (3) have been recommended for long-term hospitalisation that would require more than a 3-week stay in the hospital; (4) underwent a surgical procedure within the previous 8 weeks; (5) have back surgery planned within the next 3 months; (6) are using a spinal cord stimulator; or (7) have lower back pain attributable to a recognisable, specific pathology, including...
spinal infection, cancer, fracture or inflammatory spondylarthropathies, consistent with the NIH Task Force on research standards for cLBP.\textsuperscript{27}

Screening process

The screening process starts with either a referral from physicians at our recruitment sites or the Deep 6 AI patient cohort programme. Study brochures will be provided to all recruitment sites. The patient’s EHR will be used to help screen for eligibility as follows:

- Preferred language and age will be extracted from patient summary page.
- Presence of cLBP will be extracted from physician notes and will be verified with the participant.
- Presence of exclusions will be extracted from the ‘problem list’ and will be verified with the participant.

Participants identified as eligible will be emailed an IRB-approved recruitment letter explaining the study and an informational study brochure; recipients may opt-out of further contact by replying to this email. Those who do not opt-out will be called by a study coordinator who will verify remaining eligibility criteria. On verification of eligibility during this initial call, the consent form will be sent via REDCap by the study coordinator.

On receipt of their signed consent form and prior to randomisation, participants will be enrolled into the screener week phase of the study. The screener week was designed to ascertain willingness and ability to respond to survey questionnaires delivered by email and includes a daily electronic, one-item pain intensity question that participants are required to respond to. Participant must also complete the baseline survey questionnaires during screening week. A screen failure is defined as a participant who completed fewer than 86 of 108 items (80%) of the survey set provided halfway through the screener week and fewer than five of the seven pain diary questions also sent that week. Those with a partial survey completion or missing two daily pain intensity items will be sent a reminder email with a link to complete the survey to remain eligible. Once the patient completes the screener week, an unblinded group of coordinators will randomise them and support them throughout the study. Two study coordinators will monitor survey completion across the three arms and provide technical support as needed throughout the active study period. Patients will also receive a telephone number and email address to contact support staff.

An unblinded research coordinator will contact participants on receiving delivery confirmation of the study devices to provide onboarding instructions. Subsequent phone calls can be made to participants from coordinators to help participants complete the study. The diagram in figure 1 provides an overview of the study. Throughout the trial, participants and care providers are blinded to the intervention and the VR programs are described as either A, B or C with general terminology that applies to all three groups such as ‘nature content’. Participants will be unblinded on study completion.

Interventions and controls

On successful completion of the screener week, patients will be randomised and sent an all-in-one VR headset, the PICO G2 4k (Shenzen, China) and a biometric wristband (Fitbit Charge 4). We will include instructions for operating both the Fitbit and the PICO G2 4k device. Any headphones that are handled by staff will be sanitised by cleaning the fabric surfaces with Virex, the plastic housing with Sani-Wipes and the glass lenses with alcohol-based lens cleaner followed by a 1-min ultraviolet light treatment using Cleanbox (Carlsbad, California). The VR device will then be mailed to the participant’s preferred address, and an email will be sent to them with a FedEx tracking number and a link to YouTube videos designed to help familiarise participants with the equipment. All three interventions will include 56 modules with a defined sequence of daily sessions. Once they complete the schedule of content sequentially, participants can repeat the experiences as many times as desired. Adherence to the intervention will be monitored by self-reported use in weekly surveys. If the answer is ‘0 times’ they are asked for a reason (for a full list of options, see online supplemental file 1 for the list of reasons).

Sleep and motion tracking data from the Fitbit Charge 4 device will be aggregated by Fitabase (San Diego, California), HIPAA compliant, IRB approved, cloud-based software that maintains secure databases and keeps data private. Participants are allowed to undergo any concomitant treatment prescribed by their provider outside of those listed in exclusion criteria. Participants are allowed to discontinue the intervention at any time.

Intervention 1: skills-based VR (EaseVRx)

All VR programs in the study were developed by AppliedVR (Los Angeles, California). The skills-based VR program, called EaseVRx, incorporates evidence-based principles of CBT, mindfulness meditation and physiologic biofeedback therapy using embedded biometric sensors. EaseVRx combines psychoeducation, pain education, breathing training, relaxation exercises and executive functioning games to provide a mind-body approach toward living better with chronic pain (see figure 2 for details). The standardised, prescriptive and reproducible 56-day programme delivers a combination of skills training and CBT-related treatments through scheduled daily virtual experiences. An earlier version of this programme was used in a recently published randomised trial comparing it to an audio control of the same programme.\textsuperscript{28} Each VR experience lasts from 2 to 16 min, with an average duration of 6 min.

Intervention 2: distraction-based VR (EaseVRx-Distraction)

EaseVRx-Distraction has the same number of experiences, the same approximate duration of experiences and a user interface identical to that of EaseVRx, with a linear, prescribed sequence of experiences. The key difference is that instead of offering a variety of VR experiences including education, games and breath biofeedback,
EaseVRx-Distraction includes only 360-degree videos (also present in EaseVRx). Portions of this programme were used in our previous studies to reduce pain among hospitalised patients. This removes the effect of education and skills-based training while preserving the immersive experience of 360-degree VR.

**Placebo control: sham VR (EaseVRx-Sham)**

EaseVRx-Sham software includes two-dimensional nature footage accompanied by emotionally neutral music, rather than the 360-degree, three-dimensional, interactive content specifically selected for effectiveness. The experience of using EaseVRx-Sham is similar to watching a large-screen television in a dark room, but it is neither interactive nor immersive. EaseVRx-Sham has the same number and duration of experiences as EaseVRx, and the functionality of the user interface used to access the experiences is the same. The user interface was modified to remove aspects that were added for therapeutic benefit. Modifications include: a solid grey background instead of a colourful one as in other two arms of the study, the same solid grey background for the loading scene and removal of the background music.

**Study outcome measures**

The primary, secondary and tertiary outcomes are provided in table 1. All PROs in table 2 have cited high reliability and validity. All PROs will be collected biweekly throughout the study as well as at baseline; Patient-Reported Outcomes Measurement Information System Pain Interference (PROMIS-PI) will be collected weekly for the first 30 days. All measures required by NIH Task Force on research standards for cLBP minimum-required data set will be assessed at baseline and at end of study.

Four VR specific questionnaires will also be sent throughout the study. The Immersive Tendency Questionnaire and a customised motion sickness propensity assessment will be delivered during the screener week. The Simulator Sickness Questionnaire will be administered at day 1 to quantify the severity of initial side effects from VR headset use along with the presence scale to...
<table>
<thead>
<tr>
<th>Description of Category</th>
<th>Screenshot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interoceptive:</strong> These modules are designed to help the user understand and perceive what is happening inside the body. Within this biofeedback platform, changes in the observed environment reflect a progressively enhanced state of relaxation.</td>
<td><img src="https://via.placeholder.com/150" alt="Screenshot" /></td>
</tr>
<tr>
<td><strong>Education:</strong> These modules 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 of these education modules is for users to develop self-management skills and strategies to manage their response to pain.</td>
<td><img src="https://via.placeholder.com/150" alt="Screenshot" /></td>
</tr>
<tr>
<td><strong>360-degree videos:</strong> These videos provide high-quality 360 videos with voiceovers, music, and sound effects that are designed to maximize user relaxation and engagement.</td>
<td><img src="https://via.placeholder.com/150" alt="Screenshot" /></td>
</tr>
<tr>
<td><strong>Game modules:</strong> Games are designed to maximize distraction and engagement, thereby increasing the cognitive load on patients and decreasing their perception of pain.</td>
<td><img src="https://via.placeholder.com/150" alt="Screenshot" /></td>
</tr>
<tr>
<td><strong>Dynamic breathing:</strong> These evidence-based modules provide biofeedback training designed to enhance awareness of a user’s physiological response to pain and to self-regulate that response. 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 slow the breath to induce physiological changes that lead to relaxation.</td>
<td><img src="https://via.placeholder.com/150" alt="Screenshot" /></td>
</tr>
</tbody>
</table>

**Figure 2** Descriptions and illustrations for each of the categories of modules in the skills-based VR program. The categories of modules include: interoceptive, education, 360-degree videos, games, and dynamic breathing. VR, virtual reality.
assess how immersive and ‘real’ the virtual experience was perceived to be by the participant. A custom survey to assess for adverse events and the discontinuation of treatment will be sent weekly. At the end of the study, participants will also be asked if they had experienced VR prior to the screener week and if they would want to continue to use the device at the end of the study. The case report form for every measure is provided in the online supplemental material 1. A copy of the consent form is provided in online supplemental material 2.

Data collection
Demographic data (date of birth, age, sex, height, weight) will be extracted from the EHR. To assess comorbidities through the Charlson Comorbidity Index (CCI) calculation, International Classification of Diseases, Tenth Revision (ICD-10) codes will be collected from the EHR at day 1 and day 90. All prescription data will be extracted from the EHR and supplemented by data from the California database for scheduled prescriptions called the Controlled Substance Utilization Review and Evaluation System and will include opioid prescriptions from 90 days before enrolment until 90 days after completion of the study. Variables collected continuously by the wearable devices on the patients are provided below in table 2.

If subjects do not complete the surveys, they will be sent up to three reminder prompts. The complete schedule of measurements is provided in table 3. Participants will be eligible for up to US$225 in Amazon electronic gift cards throughout the study. After completing 80% of the first month of surveys they will be sent a US$25 Amazon card and another US$25 after 75% of the second month of surveys is completed. Once 80% of surveys in the third month are completed and the equipment returned, participants will be sent a US$175 Amazon card along with recommendations for VR programs they can use after the study.

Monitoring plan
The National Institute of Arthritis and Musculoskeletal and Skin Diseases created a data safety monitoring board (DSMB) composed of seven researchers from outside institutions. No DSMB members are otherwise involved with the study. Protocol modifications will be communicated to the DSMB and the IRB. Adverse events will be assessed on day 1 and weekly throughout the study. Monthly enrolment data will be sent to an executive secretary (Navitas Life Sciences). Virtual meetings with the DSMB are held on a biannual basis. Data Safety Monitoring (DSM) reports are submitted 2 weeks before each meeting.

Statistical analysis
Analysis of primary, secondary and tertiary (exploratory) endpoints
All statistical analyses will be performed using SAS V.9.3 or higher (SAS Institute), R pack3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) or Stata V.14 or higher (StataCorp LLC). Study statisticians will be blinded to study arm; data sets will be labelled 0, 1 and 2 by the unblinded research coordinators. For the primary endpoint and all secondary endpoints, both distraction VR therapy and skills-based VR therapy will be compared with sham VR therapy using a linear mixed model repeated measures (MMRM) analysis. Repeated measures will include changes from baseline PROMIS-PI

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**Table 1** Primary, secondary and tertiary (exploratory) outcomes

<table>
<thead>
<tr>
<th>Name</th>
<th>Time frame</th>
<th>Type</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS Pain Interference (8 item)</td>
<td>30 days</td>
<td>Primary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>PROMIS Pain Interference (8 item)</td>
<td>60 days and 90 days</td>
<td>Secondary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>Pain Catastrophizing Scale Short Form (6 item)</td>
<td>90 days</td>
<td>Secondary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>PROMIS Anxiety (4a item)</td>
<td>90 days</td>
<td>Secondary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>PROMIS Sleep Disturbance (6a item)</td>
<td>90 days</td>
<td>Secondary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>Milligram Morphine Equivalent</td>
<td>90 days</td>
<td>Secondary outcome</td>
<td>EMR/CURES</td>
</tr>
<tr>
<td>PROMIS Physical Function (6b item)</td>
<td>90 days</td>
<td>Tertiary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>PROMIS Depression (4a item)</td>
<td>90 days</td>
<td>Tertiary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>Patients’ Global Impression of Change</td>
<td>90 days</td>
<td>Tertiary outcome</td>
<td>REDCap</td>
</tr>
<tr>
<td>Fitbit weekly total steps</td>
<td>90 days</td>
<td>Tertiary outcome</td>
<td>Fitbase</td>
</tr>
<tr>
<td>Fitbit weekly total time asleep and sleep efficiency</td>
<td>90 days</td>
<td>Tertiary outcome</td>
<td>Fitbase</td>
</tr>
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**Table 2** Variables collected by wearable devices

<table>
<thead>
<tr>
<th>Device/source</th>
<th>Variable</th>
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</thead>
<tbody>
<tr>
<td>Charge 4/Fitabase</td>
<td>Total steps per day</td>
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<td></td>
<td>Total minutes of sleep per day</td>
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<tr>
<td></td>
<td>Sleep efficiency (minutes as sleep/ (minutes asleep-time in bed awake))</td>
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<tr>
<td>Pico G2 4K/</td>
<td>Content selected</td>
</tr>
<tr>
<td>AppliedVR</td>
<td>Session duration in seconds</td>
</tr>
</tbody>
</table>
### Table 3 Complete schedule of assessment

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Pre-screening</th>
<th>Screening week day -8 to -2</th>
<th>Enrolment day -1 to 0</th>
<th>Day 1 (+6 days)</th>
<th>Day 7 (+6 days)</th>
<th>Day 15 (+6 days)</th>
<th>Day 21 (+6 days)</th>
<th>Day 30 (+6 days)</th>
<th>Day 45 (+6 days)</th>
<th>Day 60 (+6 days)</th>
<th>Day 75 (+6 days)</th>
<th>Day 90 (+6 days)</th>
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</thead>
<tbody>
<tr>
<td>Pain Intensity Journal(^a) (seven days)</td>
<td>X</td>
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<tr>
<td>Intervention: participant uses VR therapy programme and wears Fitbit Charge 4 watch</td>
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<tr>
<td>NIH HEAL minimum data set</td>
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<tr>
<td>Immersive Tendency Questionnaire(^35) and Motion Sickness Propensity Survey(^36)</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Treatment expectation question</td>
<td>X</td>
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<tr>
<td>Simulator Sickness Questionnaire(^37) and Presence Survey(^44)</td>
<td></td>
<td>X</td>
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<tr>
<td>Primary outcome: PROMIS Pain Interference(^45)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Discontinuation of Treatment Questionnaire</td>
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Continued
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Pre-screening</th>
<th>Screening week day −8 to −2</th>
<th>Enrolment day −1 to 0</th>
<th>Day 1 (+6 days)</th>
<th>Day 7 (+6 days)</th>
<th>Day 15 (+6 days)</th>
<th>Day 21 (+6 days)</th>
<th>Day 30 (+6 days)</th>
<th>Day 45 (+6 days)</th>
<th>Day 60 (+6 days)</th>
<th>Day 75 (+6 days)</th>
<th>Day 90 (+6 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS Physical Function, Anxiety, Depression, Sleep disturbance, Pain intensity/interference with enjoyment of life/interference with general activity, PCS-6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>EMR data: Charlson Comorbidity Index, CURES and EMR: prescription data</td>
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<td>X</td>
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<tr>
<td>Perceived study arm question and treatments over last 90 days question</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>PHQ-2, GAD-2, PGIC, TAPS(1/2)</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Event assessment: AE, SAE, UP reporting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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AE, adverse event; CURES, Controlled Substance Utilization Review and Evaluation System; EMR, Electronic Medical Record; GAD-2, Generalised Anxiety Disorder 2-item; HEAL, Helping to End Addiction Long-term; ITQ, Immersive Tendency Questionnaire; NIH, National Institute of Health; PCS-SF, Pain Catastrophizing Scale-Short Form 6; PEG, pain, enjoyment, general activity; PGIC, patient global impression of change; PHQ-2, Patient Health Questionnaire-2; PROMISE, Patient-Reported Outcomes Measurement Information System; SAE, serious adverse event; TAPS, tobacco, alcohol, prescription medication, and other substance use; UP, unanticipated problem; VR, virtual reality.
t-score and those obtained at days 7, 15 and 21. Models will include fixed categorical effects for treatment, week, their interaction; baseline PROMIS-PI t-score will be included as a covariant. If skills-based VR and sham VR are found to differ, a third comparison will be made between skills-based VR therapy and distraction VR therapy.

For these models, we will estimate least squares means, SEs, treatment differences (in least squares means) and 95% CIs for each time period. Primary inference will rely on treatment comparison of least squares means for day 30, and a p value will be presented for this time period only. The null hypothesis there is no mean difference in the primary endpoint between the treatment groups and the sham control group. Similar analyses will be conducted for all secondary endpoints.

Efficacy and safety data summaries and analyses will be performed by study arm using intent-to-treat (ITT). The number and percentage of patients randomised, patient population (ITT) and treatment status (completed, discontinued/withdrawn) will be summarised. Reasons for discontinuation/withdrawal will be reported. An exploratory, per protocol (PP) analysis will focus on patients who use the assigned intervention on at least 50% of days during the first 30-day period. Usage meta-data on the headsets will provide the data needed for the PP definition. No formal interim analysis or interim statistical testing for treatment comparisons is planned.

If the primary or key secondary endpoint is missing in >15% of patients in either treatment group, then the pattern of baseline covariates with missing values will be examined using the method of Little and if data are not missing completely at random, missing values will be imputed using fully conditional specification with the multivariate imputation by chained equations algorithm under the missing at random assumption.

Subgroup analysis
Subgroup analyses are planned for changes from baseline PROMIS-PI using linear MMRM analysis to test for treatment and subgroup interactions. Interactions significant at p<0.10 will be flagged for further assessment. Generally, models will include fixed categorical effects for treatment and week and their interaction, subgroup and treatment by subgroup interaction. Descriptive statistics of observed and changes from baseline PROMIS-PI t-score will be presented by treatment and week within each subgroup.

Subgroups to be analysed:
- Dosage of VR (min/week).
- Previous experience with VR.
- Immersive tendency questionnaire score.
- Presence score.
- Patient comorbidities (CCI).
- History of spinal surgery.
- Pain severity and duration.
- Sociodemographics (ie, age, sex, race, ethnicity, marital status, education).
- Other treatments

Sample size
The PROMIS-PI scale has a SD of 10 and a mean of 50. Using an inflated SD of 11.83 (to accommodate correlation of repeated measures within individual) we estimated power by simulating 10 000 trial replicates and testing the null hypothesis versus the alternative hypothesis. To maintain familywise error rate at 0.05, a two-sample t-test is used to compare the control arm to each treatment arm and the test is declared statistically significant if the p value of the two-sided test is less than 0.025. Under the alternative hypothesis, data from 120 patients in each of the three arms achieved 843% power to detect a clinically meaningful effect of a change in five units of the PROMIS score. Type I error rate is 0.0469 and the SD of the PROMIS scores difference is 11.83 assuming a correlation coefficient of 0.3 between baseline and 30 days PROMIS scores. With correlation of 0.2, power is 80% to detect the same difference. Any participants who withdraw or are withdrawn or discontinued on or prior to day 30 will be replaced.

Patient and public involvement
This protocol was developed in partnership with a chronic pain patient advocate. This coauthor (TN) provided input on a weekly basis during the development of protocol and will be involved in overseeing conduct of the study together with the research team. Our patient partner helped develop custom surveys and provided input on the burden surveys and interventions might have on participants. The results will be emailed to all participants at the end of the study.

Ethics and dissemination
This trial has been approved by the IRB of CSHS. All participants enrolled in the study will provide written informed consent. The results will be disseminated through peer-reviewed scientific journals. The recruiting providers and participants will be emailed the results at the end of the study. Authorship eligibility is based on significant contribution to the study and review of the manuscript. BACPAC investigators will have access to final data set.

Trial status
Participant recruitment started in September 2020 and is expected to end in September 2023. At the time of this writing in May 2021, 96 participants have been randomised.
Author affiliations
1Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA
2Department of Biomedical Sciences, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea
3American Chronic Pain Association, Rocklin, California, USA
4Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA
5Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California, USA
6Department of Orthopedics, Cedars-Sinai Medical Center, Los Angeles, California, USA
7Department of Psychiatry and Behavioral Neurosciences, Cedars-Sinai Medical Center, Los Angeles, California, USA

Twitter Brandon Birckhead @bjbirckhead and Brennan Spiegel @BrennanSpiegel

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Contributors
Study design: BB, GF, BS, SE, GA, RG, TD, KM, XL, K-SY, JTB, MI, SV, JT, TN, MT, LR, KmKo, MV and ID. Acquisition of participants: MI, SV, JT and LR. Acquisition of data: SE, GA, RG, TD and KM. Drafting manuscript: BB. Critical analysis: BS, GA, RG, TD, KM, XL, K-SY, JTB, MI, SV, TN, JT, MT, LR, KmKo, MV, and ID. Statistical analysis planning and revision of the manuscript for important intellectual content: GF, BS, SE, GA, RG, TD, KM, XL, K-SY, JTB, MI, SV, TN, JT, MT, LR, KmKo, MV and ID. Study supervision: BS. Administrative, technical or material support: SE and GA. All authors have approved the submitted version of the manuscript and agreed to be accountable for their own contribution.

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Competing interests
BB worked as a research consultant for AppliedVR for an independent clinical trial. All other authors have no conflict of interest to declare.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Supplemental material
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ORCID id
Brandon Birckhead http://orcid.org/0000-0002-5822-7318

REFERENCES
SUPPLEMENTARY FILES:

Supplementary File 1: Case report forms
Baseline Demographics

*=HEAL required questions

1. 1. *Gender identity  □ Male  □ Female  □ Unknown  Other, Specify: ____________

2. *What is the highest level of education you have completed?
   □ Did not complete Secondary School or Less than High School
   □ Some Secondary School or High School Education
   □ High School or Secondary School Degree Complete
   □ Associate’s or Technical Degree Complete
   □ Doctoral or Postgraduate Education

3. *What is your current employment status?
   □ Full-time employment
   □ Not employed
   □ Part-time employment

4. *What category best describes your current relationship status?
   □ Divorced
   □ Married
   □ Never Married
   □ Separated
   □ Widowed
   □ Domestic Partner

5. Including yourself, how many people live in your household? _________

6. *How long have you had the type of pain for which you are enrolled in this study? (Please list the number of months) __________

7. Is your low back pain more severe than pain in other parts of your body?
   a) Yes
   b) No
   c) Not sure

8. Have you ever had a low-back operation?
   a) Yes, one operation
   b) Yes, more than one operation
   c) No

9. If yes, when was your last back operation?
   a) Less than 6 months
   b) More than 6 months but less than 1 year ago
   c) Between 1 and 2 years ago
   d) More than 2 years ago
10. Did any of your back operations involve a spinal fusion? (also called an arthrodesis?)
   a) Yes
   b) No
   c) Not sure

11. Have you been off work or unemployed for 1 month or more due to low-back pain?
   a) Yes
   b) No
   c) Does not apply

12. Have you filed or been awarded a worker’s compensation claim related to your back problem?
   a) Yes
   b) No
   c) Does not apply

13. Are you involved in a lawsuit or legal claim related to your back problem?
   a) Yes
   b) No
   c) Not sure

14. *Have you ever applied for, or received, disability insurance for your pain condition?
   a) Yes
   b) No

15. *What is your annual household income from all sources?
   - Less than $10,000
   - $10,000 - $24,000
   - $25,000 - $34,999
   - $35,000 - $49,999
   - $50,000 - $74,999
   - $75,000 - $99,999
   - $100,000 - $149,999
   - $150,000 - $199,999
   - $200,000 or more
   - Prefer not to answer
Minimum Dataset: Outcomes Assessment

Completed at baseline and 3 months

*=HEAL-required CDE

Pain Duration and Frequency

1. How long has low-back pain been an ongoing problem for you?
   a) <3 months
   b) 3-6 months
   c) 6 months-1 year
   d) 1 to 5 years
   e) More than 5 years

2. How often has low-back pain been an ongoing problem for you over the past 6 months?
   a) Every day or nearly every day in the past 6 months
   b) At least half the days in the past 6 months
   c) Less than half the days in the past 6 months

Pain Location

3. Has back pain spread to your buttock or thigh during the past 2 weeks?
   a) Yes
   b) No
   c) Not sure

4. Has back pain spread below your knee during the past 2 weeks?
   a) Yes
   b) No
   c) Not sure

Widespread Pain

5. Do you have chronic pain the following areas?
   a) Head or face (Yes/No)
   b) Right hand, arm, or shoulder (Yes/No)
   c) Left hand, arm, or shoulder (Yes/No)
   d) Right buttock, leg, or foot (Yes/No)
   e) Left buttock, leg, or foot (Yes/No)
   f) Chest, abdomen, or pelvis (Yes/No)
   g) Neck or upper back (Yes/No)
Pain Somatization

6. During the past 4 weeks, how much have you been bothered by...
   a) Stomach pain
   b) Not bothered at all
   c) Bothered a little
   d) Bothered a lot
   e) Headaches
   f) Not bothered at all
   g) Bothered a little
   h) Bothered a lot

Low-Back Pain Specific Pain Intensity

7. How would you rate your low-back pain on average?
   _0_1_2_3_4_5_6_7_8_9_10
   No Pain                    Worst imaginable pain

Current Opioid Use

8. Are you currently taking any opioid medications on a daily basis? (Opioid or narcotic medications include prescription medications such as Vicodin, Lortab, Narco, Hydrocodone, codeine, Tylenol #3 or #4, Fentanyl, Duragesic, MS Contin, Percocet, OxyContin, oxycodone, Morphine, methadone, tramadol, Ultram, Diluadid)
   a) Yes
   b) Not
   c) Not Sure

Sleep Duration*

1. During the past month, how many hours and minutes of actual sleep did you get at night? (This may be different than the number of hours and minutes you spent in bed)
   ____ hours and ____ minutes of sleep per night
Pain Intensity Journal (7 days)

Rate your average [back] pain today on a scale from 0-10, where 0 means no pain and 10 means the worst pain imaginable.

0 1 2 3 4 5 6 7 8 9 10
No Pain Worst imaginable pain
Motion Sickness Propensity Questionnaire

1. I am susceptible to sickness induced by video or computer games.
   a) True
   b) False

2. I get motion sickness.
   a) True
   b) False
Immersive Tendency Questionnaire


1. Do you ever get extremely involved in projects that are assigned to you by your boss or your instructor, to the exclusion of other tasks?

   ___1___2___3___4___5___6___7
   Never Occasionally Often

2. How easily can you switch your attention from the task in which you are currently involved to a new task?

   ___1___2___3___4___5___6___7
   Not so easily Fairly Often

3. How frequently do you get emotionally involved (angry, sad, or happy) in the news stories that you read or hear?

   ___1___2___3___4___5___6___7
   Never Occasionally Often

4. How well do you feel today?

   ___1___2___3___4___5___6___7
   Not well Pretty well Excellent

5. Do you easily become deeply involved in movies or TV dramas?

   ___1___2___3___4___5___6___7
   Never Occasionally Often

6. Do you ever become so involved in a television program or book that people have problems getting your attention?

   ___1___2___3___4___5___6___7
   Never Occasionally Often

7. How mentally alert do you feel at the present time?

   ___1___2___3___4___5___6___7
   Not alert Moderately Alert Fully Alert

8. Do you ever become so involved in a television program or book that people have problems getting your attention?

   ___1___2___3___4___5___6___7
   Never Occasionally Often

9. How frequently do you find yourself closely identifying with the characters in a storyline?

   ___1___2___3___4___5___6___7
10. Do you ever become so involved in a video game that it is as if you are inside the game rather than moving a joystick and watching the screen? 

   Never  Occasionally  Often 

   ___1___2___3___4___5___6___7

11. On average, how many books do you read for enjoyment in a month? 

   ___1___2___3___4___5___6___7

12. What kind of books do you read most frequently? 

   1, Spy novels | 2, Adventure novels | 3, Westerns | 4, Biographies | 5, Fantasies | 6, Romance novels | 7, Mysteries | 8, Autobiographies | 9, Science fiction | 10, Historical novels | 11, Other fiction | 12, Other non-fiction

13. How physically fit do you feel today? 

   ___1___2___3___4___5___6___7

   Not fit  Moderately fit  Extremely fit

14. How good are you at blocking out external distractions when you are involved in something? 

   ___1___2___3___4___5___6___7

   Not very good  Somewhat good  Very good

15. When watching sports, do you ever become so involved in the game that you react as if you were one of the players? 

   ___1___2___3___4___5___6___7

   Never  Occasionally  Often

16. Do you ever become so involved in a daydream that you are not aware of things happening around you? 

   ___1___2___3___4___5___6___7

   Never  Occasionally  Often

17. Do you ever have dreams that are so real that you feel disoriented when you awake? 

   ___1___2___3___4___5___6___7

   Never  Occasionally  Often

18. When playing sports, do you become so involved in the game that you lose track of time? 

   ___1___2___3___4___5___6___7

   Never  Occasionally  Often

19. Are you easily disturbed when working on a task? 

   ___1___2___3___4___5___6___7

   Never  Occasionally  Often
20. How well do you concentrate on enjoyable activities?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

21. How often do you play arcade or video games? (FOTEN should be taken to mean every day or every two days, on average.)
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

22. How well do you concentrate on disagreeable tasks?
   ___1___2___3___4___5___6___7
   Not well       Moderately well Very well

23. Have you ever gotten excited during a chase or fight scene on TV or in the movies?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

24. To what extent have you dwelled on personal problems in the last 48 hours?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

25. Have you ever gotten scared by something happening on a TV show or in a movie?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

26. Have you ever remained apprehensive or fearful long after watching a scary movie?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

27. Do you ever avoid carnival or fairground rides because they are too scary?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

28. How frequently do you watch TV soap operas or docu-dramas?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often

29. Do you ever become so involve din doing something that you lose all track of time?
   ___1___2___3___4___5___6___7
   Never          Occasionally    Often
Simulator Sickness Questionnaire
Kennedity, Lane, Berbaym, & Lilienthal (1993)**


Instructions: Circle how much each symptom below is affecting you **right now.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Eye strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Difficulty focusing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Salivation increasing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Sweating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Difficulty concentrating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. &lt;&lt; Fullness of the head &gt;&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Blurred vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Dizziness with eyes open</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Dizziness with eyes closed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. *Vertigo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. **Stomach awareness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Burping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Vertigo is experience as loss of orientation with respect to vertical upright.

** Stomach awareness is usually used to indicate a feeling of discomfort which is just short of nausea.
Presence Scale Questionnaire

On a five-point scale (1 = not at all; 5 = extremely), designate the degree to which you feel presence.

1. To what extent did you feel like you were inside the virtual world?
   
   ___1___2___3___4___5
   
   Not at all  Extremely

2. To what extent did you feel immersed in the virtual world?
   
   ___1___2___3___4___5
   
   Not at all  Extremely

3. To what extent did you feel surrounded by the virtual world you saw and heard?
   
   ___1___2___3___4___5
   
   Not at all  Extremely

4. How much did it feel as if you visited another place?
   
   ___1___2___3___4___5
   
   Not at all  Extremely

5. How much was the virtual world like the real world?
   
   ___1___2___3___4___5
   
   Not at all  Extremely

6. To what extent were you distracted by noises in the physical world while you were inside the virtual world?
   
   ___1___2___3___4___5
   
   Not at all  Extremely
**PROMIS Pain Interference – Short Form 8a**

**PROMIS® Item Bank v1.0 – Pain Interference – Short Form 8a**

**Pain Interference – Short Form 8a**

Please respond to each question or statement by marking one box per row.

<table>
<thead>
<tr>
<th>In the past 7 days...</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAIN05</strong></td>
<td>How much did pain interfere with your daily activities?</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN12</strong></td>
<td>How much did pain interfere with work around the home?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN01</strong></td>
<td>How much did pain interfere with your ability to participate in social activities?</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN34</strong></td>
<td>How much did pain interfere with your household chores?</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN13</strong></td>
<td>How much did pain interfere with the things you usually do for fun?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN06</strong></td>
<td>How much did pain interfere with your enjoyment of social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN36</strong></td>
<td>How much did pain interfere with your enjoyment of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>PAIN13</strong></td>
<td>How much did pain interfere with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
# PROMIS Physical Function – Short Form 6b

PROMIS® Item Bank v2.0 – Physical Function – Short Form 6b

## Physical Function – Short Form 6b

Please respond to each question or statement by marking one box per row.

<table>
<thead>
<tr>
<th>Question</th>
<th>Without any difficulty</th>
<th>With a little difficulty</th>
<th>With some difficulty</th>
<th>With much difficulty</th>
<th>Unable to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to do chores such as vacuuming or yard work? ..................</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Are you able to go up and down stairs at a normal pace? .....................</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Are you able to go for a walk of at least 15 minutes? .......................</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Are you able to run errands and shop? ...........</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Does your health now limit you in doing two hours of physical labor? .......</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
PROMIS Emotional Distress Anxiety – Short Form 4a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

<table>
<thead>
<tr>
<th>Item</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>I felt fearful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I found it hard to focus on anything other than my anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My worries overwhelmed me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I felt uneasy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past 7 days...</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>--------</td>
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<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>I felt worthless</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I felt helpless</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I felt depressed</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>I felt hopeless</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
PROMIS Sleep Disturbance – Short Form 6a

Sleep Disturbance – Short Form 6a

Please respond to each question or statement by marking one box per row.

<table>
<thead>
<tr>
<th>In the past 7 days...</th>
<th>Very poor</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>My sleep quality was</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In the past 7 days...</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>My sleep was refreshing</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>I had a problem with my sleep</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I had difficulty falling asleep</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My sleep was restless</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I tried hard to get to sleep</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
PEG – Pain Screening Tool

Select the one number that describes your pain.

1) What number best describes your pain on average in the past week?

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

2) What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely
Interfere

3) What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely
Interfere
Pain Catastrophizing Questionnaire – Short Form 6-item

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are six statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

When I’m in pain ...

1. It’s awful and I feel that it overwhelms me

0  1  2  3  4
Not at all  To a slight degree  To a moderate degree  To a great degree  All the time

2. I feel I can’t stand it anymore

0  1  2  3  4
Not at all  To a slight degree  To a moderate degree  To a great degree  All the time

3. I become afraid that the pain will get worse

0  1  2  3  4
Not at all  To a slight degree  To a moderate degree  To a great degree  All the time

4. I keep thinking about how much it hurts

0  1  2  3  4
Not at all  To a slight degree  To a moderate degree  To a great degree  All the time

5. I keep thinking about how badly I want the pain to stop

0  1  2  3  4
Not at all  To a slight degree  To a moderate degree  To a great degree  All the time
6. I wonder whether something serious may happen

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not at all</td>
<td>To a slight degree</td>
<td>To a moderate degree</td>
<td>To a great degree</td>
<td>All the time</td>
</tr>
</tbody>
</table>
Pain Health Questionnaire – 2 (PHQ-2)

Over the last 2 weeks, how often have you been bothered by the following problems?

1. Little interest or pleasure in doing things

   0 1 2 3

   Not at all  Several days  More than half the days  Nearly every day

2. Feeling down, depressed, or hopeless

   0 1 2 3

   Not at all  Several days  More than half the days  Nearly every day
Generalized Anxiety Disorder-2 (GAD-2)

Over the last 2 weeks, how often have you been bothered by the following problems?

1. Feeling nervous, anxious, or on edge
   - 0 Not at all
   - 1 Several days
   - 2 More than half the days
   - 3 Nearly every day

2. Not being able to stop or control worrying
   - 0 Not at all
   - 1 Several days
   - 2 More than half the days
   - 3 Nearly every day
Patient Global Impression of Change (PGIC)

Since the start of intervention, my overall pain is ….

_1 – Very much improved
_2 – Much improved
_3 – Minimally improved
_4 – No Change
_5 – Minimally worse
_6 – Much worse
_7 – Very much worse
Event Assessment

Day 1:

1. Have you experienced anything different during or after use of the VR headset?
   a. Yes
   b. No
   c. Other

2. If Yes or Other, please describe the event. A research staff member will follow-up with you about this event as soon as possible.
   - [Open Text Box]

15-day interval, end of study:

3. During the past 14 days, have you experienced anything different during or after use of the VR headset?
   a. Yes
   b. No
   c. Other

4. If Yes or Other, please describe the event. A research staff member will follow-up with you about this event as soon as possible.
   - [Open Text Box]
Custom Questions

Screener Week

1. Have you experienced virtual reality before?
   a. Yes
   b. No

End of study survey

2. Would you have wanted to continue to use the device?
   a. Yes
   b. No
TAPS Tool Part 1

NIDA Clinical Trials Network
The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool

TAPS Tool Part 1  Web Version: 2.0, 4.00, 09-19-17

General Instructions:
The TAPS Tool Part 1 is a 4-item screening for tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year. Question 2 should be answered only by males and Question 3 only by females. Each of the four multiple-choice items has five possible responses to choose from. Check the box to select your answer.

Visit number:

1. In the PAST 12 MONTHS, how often have you used any tobacco product (for example, cigarettes, e-cigarettes, cigars, pipes, or smokeless tobacco)?
   - Daily or Almost Daily
   - Less Than Monthly
   - Weekly
   - Never
   - Monthly

2. In the PAST 12 MONTHS, how often have you had 5 or more drinks containing alcohol in one day? One standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor. (Note: This question should only be answered by males).
   - Daily or Almost Daily
   - Less Than Monthly
   - Weekly
   - Never
   - Monthly

3. In the PAST 12 MONTHS, how often have you had 4 or more drinks containing alcohol in one day? One standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor. (Note: This question should only be answered by females).
   - Daily or Almost Daily
   - Weekly
   - Less Than Monthly
   - Never
   - Monthly

4. In the PAST 12 MONTHS, how often have you used any drugs including marijuana, cocaine or crack, heroin, methamphetamine (crystal meth), hallucinogens, ecstasy/MDMA?
   - Daily or Almost Daily
   - Weekly
   - Less Than Monthly
   - Never
   - Monthly

5. In the PAST 12 MONTHS, how often have you used any prescription medications just for the feeling, more than prescribed or that were not prescribed for you? Prescription medications that may be used this way include: Opiate pain relievers (for example, OxyContin, Vicodin, Percocet, Methadone) Medications for anxiety or sleeping (for example, Xanex, Ativan, Klonopin) Medications for ADHD (for example, Adderall or Ritalin)
   - Daily or Almost Daily
   - Weekly
   - Less Than Monthly
   - Never
   - Monthly
TAPS Tool Part 2

NIDA Clinical Trials Network
The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool

TAPS Tool Part 2

General Instructions:
The TAPS Tool Part 2 is a brief assessment for tobacco, alcohol, and illicit substance use and prescription medication misuse in the PAST 3 MONTHS ONLY. Each of the following questions and sub-questions has two possible answer choices- either yes or no. Check the box to select your answer.

1. In the PAST 3 MONTHS, did you smoke a cigarette containing tobacco? □ Yes □ No
   If "Yes", answer the following questions:
   a. In the PAST 3 MONTHS, did you usually smoke more than 10 cigarettes each day? □ Yes □ No
   b. In the PAST 3 MONTHS, did you usually smoke within 30 minutes after waking? □ Yes □ No

2. In the PAST 3 MONTHS, did you have a drink containing alcohol? □ Yes □ No
   If "Yes", answer the following questions:
   a. In the PAST 3 MONTHS, did you have 4 or more drinks containing alcohol in a day?*(Note: This question should only be answered by females.) □ Yes □ No
   b. In the PAST 3 MONTHS, did you have 5 or more drinks containing alcohol in a day?*(Note: This question should only be answered by males.) □ Yes □ No
   c. In the PAST 3 MONTHS, have you tried and failed to control, cut down or stop drinking? □ Yes □ No
   d. In the PAST 3 MONTHS, has anyone expressed concern about your drinking? □ Yes □ No

3. In the PAST 3 MONTHS, did you use marijuana (hash, weed)? □ Yes □ No
   If "Yes", answer the following questions:
   a. In the PAST 3 MONTHS, have you had a strong desire or urge to use marijuana at least once a week or more often? □ Yes □ No
   b. In the PAST 3 MONTHS, has anyone expressed concern about your use of marijuana? □ Yes □ No

4. In the PAST 3 MONTHS, did you use cocaine, crack, or methamphetamine (crystal meth)? □ Yes □ No
   If "Yes", answer the following questions:
   a. In the PAST 3 MONTHS, did you use cocaine, crack, or methamphetamine (crystal meth) at least once a week or more often? □ Yes □ No
   b. In the PAST 3 MONTHS, has anyone expressed concern about your use of cocaine, crack, or methamphetamine (crystal meth)? □ Yes □ No

5. In the PAST 3 MONTHS, did you use heroin? □ Yes □ No
   If "Yes", answer the following questions:
   a. In the PAST 3 MONTHS, have you tried and failed to control, cut down or stop using heroin? □ Yes □ No
b. In the PAST 3 MONTHS, has anyone expressed concern about your use of heroin? □ Yes □ No

6. In the PAST 3 MONTHS, did you use a prescription opiate pain reliever (for example, Percocet, Vicodin) not as prescribed or that was not prescribed for you? □ Yes □ No
   If “Yes”, answer the following questions:
   a. In the PAST 3 MONTHS, have you tried and failed to control, cut down or stop using an opiate pain reliever? □ Yes □ No
   b. In the PAST 3 MONTHS, has anyone expressed concern about your use of an opiate pain reliever? □ Yes □ No

7. In the PAST 3 MONTHS, did you use a medication for anxiety or sleep (for example, Xanax, Ativan, or Klonopin) not as prescribed or that was not prescribed for you? □ Yes □ No
   If “Yes”, answer the following questions:
   a. In the PAST 3 MONTHS, have you had a strong desire or urge to use medications for anxiety or sleep at least once a week or more often? □ Yes □ No
   b. In the PAST 3 MONTHS, has anyone expressed concern about your use of medication for anxiety or sleep? □ Yes □ No

8. In the PAST 3 MONTHS, did you use a medication for ADHD (for example, Adderall, Ritalin) not as prescribed or that was not prescribed for you? □ Yes □ No
   If “Yes”, answer the following questions:
   a. In the PAST 3 MONTHS, did you use a medication for ADHD (for example, Adderall, Ritalin) at least once a week or more often? □ Yes □ No
   b. In the PAST 3 MONTHS, has anyone expressed concern about your use of medication for ADHD (for example, Adderall or Ritalin)? □ Yes □ No

9. In the PAST 3 MONTHS, did you use any other illegal or recreational drug (for example, ecstasy/molly, GHB, poppers, LSD, mushrooms, special K, bath salts, synthetic marijuana ('spice'), whip-its, etc.)? □ Yes □ No
   If “Yes”, answer the following questions:
   In the PAST 3 MONTHS, what were the other drug(s) you used?

Comments:
Discontinuation of Treatment Questionnaire

1. In the last week, how many days did you use the VR headset?
   a. None of the days
   b. Some of the days
   c. Most of the days
   d. All of the days

2. Which of the following best describes why you have not used the VR headset in the last week?
   Technical problem(s) using the headset
     a. Yes
     b. No
   Unsatisfied with the program content
     a. Yes
     b. No
   VR headset is uncomfortable
     a. Yes
     b. No
   Schedule too busy to use the headset
     a. Yes
     b. No
   Pain is too high to use the headset
     a. Yes
     b. No
   The program does not relieve my pain
     a. Yes
     b. No
   Other [open text box]

3. Would it be ok for a study team member to call you and help resolve any problems with the headset?
   a. Yes
   b. No
Perceived Study Arm Question

This VR study involved randomly assigning all study participants to receive one of the following:

(1) active VR treatment for chronic pain or
(2) an intervention that did not include active VR treatment for chronic pain.

Your amazon code email that you get after returning the equipment will tell you the group you were in. Before we tell you, we would like you to guess your group assignment.

I believe that I received:

1. (1) active VR treatment for chronic pain.
2. (2) an intervention that did not include active VR treatment for chronic pain.
Treatment Expectation Question

1. I believe this treatment will help me...
   a. Not at all
   b. A little bit
   c. Somewhat
   d. Quite a bit
   e. Very much
End of study procedure Question

Since the beginning of the study, have you had any of the following procedures/treatments? (Select all that apply)

- Injections (TFESI, SNRB, ESI, Facet Block, steroid, facet joints, sacroiliac joint injections, Epidural injections, Rhizotomy, inter laminar or transforaminal injection)
- Pain Pump
- Occupational Therapy, Physical Therapy
- Aqua Therapy
- Acupuncture/acupressure
- Chiropractic procedures (adjustments)
- Massage
- TENS unit
- Radio frequency ablations (RFA)
- Cannabis related products
- Other [open text box]
Supplementary File 2: Consent Forms
CONSENT FORM FOR RESEARCH and
TEEN (13-17 YEARS OLD) ASSENT AND PARENTAL PERMISSION FORM FOR RESEARCH

Disclaimer: The following is the consent form for research.

If you are between the ages of 13 to 17, parental permission to participate in research is required and this document will serve as an assent form for research. If you are a parent/guardian of a child who may participate, “you” refers to “your child” throughout this form.

Title: RANDOMIZED-CONTROLLED TRIAL OF VIRTUAL REALITY FOR CHRONIC LOW BACK PAIN TO IMPROVE PATIENT-REPORTED OUTCOMES AND PHYSICAL ACTIVITY

SPONSOR: THE NATIONAL INSTITUTES OF HEALTH (NIH)

Principal Investigator: Brennan Spiegel, MD

Study Contact Phone Number at CSMC: (310) 423-5434

After Hours Contact (24 hours): (248) 383-5346

This research study is sponsored by the NIH. The NIH only reimburses Cedars-Sinai Medical Center for the costs associated with running the study; the NIH is not providing additional compensation to Cedars-Sinai Medical Center or the Principal Investigator for their participation in the study.

KEY INFORMATION ABOUT THIS RESEARCH STUDY

We are seeking your consent to take part in this research study. Your participation in this research is voluntary. If you choose to participate, you can stop at any time. Please consider the following summary, along with the more detailed information provided throughout this consent form.

- The purpose of this study is to assess the impact of virtual reality (VR) therapy on chronic lower back pain. We want to see if using VR therapy will improve pain management, offer additional pain relief, or be an effective alternative to traditional pain medication.

- The main procedures of this study include using a virtual reality headset every day to manage your pain for 90 days. Using the headset will take about 10 minutes each day.
You will also wear a Fitbit to collect data on your daily activity. We will also ask you to complete weekly surveys over the first 30 days, then biweekly surveys until the end of the study. Surveys will be sent via email and can be completed from a computer or smartphone (Android or iOS). **You will need to complete one week of screening surveys prior to being sent the virtual reality headset and other study materials.** If you choose to take part in this study, it will last about 90 days.

- All research studies involve some risks. Risks or discomforts from this study may include: minor psychological distress from questionnaires regarding health and employment status, and ~5% risk of “cybersickness,” presenting as short-term symptoms related to entering VR environments (vertigo, nausea, headache).

- Potential immediate benefits include reduction of chronic low back pain and overall improvements in psychological health. Potential long-term benefits include improved functionality, reduced opioid use, and improvements in overall physical health. This research will contribute to the societal knowledge about the use of digital interventions within healthcare.

- If at any point in the study you feel the need to make any changes to your prescribed medications, please talk with your prescribing physician. Making abrupt changes to medications may be unsafe and any modification in medications should occur under the guidance of your physician.

- If you choose not to participate, there may be other choices available to you. You can continue your current treatment with your providers. You will not lose any services, benefits or rights you would normally have if you choose not to participate. Please discuss your choices with the researchers.

Please take time to read this entire form and ask questions before deciding whether to participate in this study. You are encouraged to talk with family members, friends, and/or healthcare providers before you make your decision.

1. **WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?**

We are doing this study to see if using an audiovisual headset helps to manage or improve chronic lower back pain. We want to know if the use of this tool can limit the extent to which pain interferes with your life and if your overall health improves.

You are being asked to take part in this research study because you are an outpatient at Cedars- Sinai Medical Center (CSMC) with chronic lower back pain.

In this study, three different virtual reality experiences using three different software programs will be assessed for their ability to reduce pain. You will be randomized into one of three groups after the screening period. See Section 2 below for more information.

The study will enroll up to 360 people in total.
This research study is designed to use the PICO G2 Headsets and the Fitbit Charge 4 Activity Monitor. Both the VR headset and Fitbit Charge 4 activity monitor can be purchased in stores, are not currently regulated by the FDA, and pose minimal to no risks to individuals.

2. **WHAT WILL HAPPEN DURING THE STUDY?**

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as an Appendix.

The flowchart shows a timeline for research-related procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study. All procedures in this study are research-related procedures.

At the start of the study, you will be sent surveys via email. Surveys can be completed on a computer or smartphone (Android or iOS). You will be trained on how to use the VR headset, Fitbit, and any related apps required for the study.

**Overview of study:**

This is a single-blind, randomized research study with an additional screening week. Standard (routine) care will involve treatment as prescribed by your provider for your pain condition.

Your study participation will not dictate your standard treatment or care.

- **“Single-blind”** means that the researchers will know which group you are assigned to but will not tell you which group you are participating in. Your physician will also not know which group you are in.
- **“Randomized”** means that you will be assigned to a study group by chance, like flipping a coin. You will be randomized into one of three study groups and will have an equal chance of being placed in one of the three groups described below.
- **“Screening week”** means you will receive surveys every day for a week via email. Once you complete this week of surveys, you will be eligible to be randomized.

A computer will randomly assign you to a study group. This is done because no one knows if the results experienced by the participants in one study group are better, the same, or worse.
than the results experienced by participants in the other. Once you are put in one group, you cannot switch to another group. Neither you nor your doctor can choose the group in which you will be placed.

Any of these different approaches could help your condition but could also cause mild temporary side effects. This study will allow the researchers to learn whether the different software programs are better, the same, or worse than the current standard of care. Audiovisual therapy has been used in several studies at Cedars-Sinai. The results of these studies have demonstrated the device to be safe; less than 25% of patients who use the VR headset have minor, short-term side effects from the device.

If you are assigned to any group, you will be followed as you receive the care generally provided for individuals with your condition, with the addition of a wrist-worn sensor to track your physical activity, sleep quality and duration, and heart rate. This sensor is called a Fitbit. You will be asked to use the VR unit for no more than 20 minutes at least once a day and as needed during moments of pain. You will be asked to complete surveys asking questions about your pain via email.

The wrist-sensor, VR unit, and the app we install on your smartphone will collect data and periodically upload data to secure, encrypted servers at Cedars-Sinai.

You will be asked to keep your smartphone on your person and answer surveys when prompted. We will also ask you to keep the VR headset with you whenever possible and wear the sensor on your wrist at all times. You should only remove the sensor when charging the unit or prior to starting an activity that may damage the headset, such as taking a shower or swimming. In the event that any of the study equipment are lost or damaged, you will not be held responsible for the lost or damaged study equipment. However, all study equipment, whether damaged or intact, must be returned at the end of the study.

**Prescription Data**

As part of this study, we will be collecting prescription data from the Cedars-Sinai Medical Record as well as any prescription data available from the California Controlled Substance Utilization Review and Evaluation System (CURES), if relevant. CURES is a database that tracks controlled substances prescribed to patients in the state of California. Our study will request permission to obtain prescription data to assess whether there are any changes in medication use throughout the course of the study. The data will be collected from 90 days before enrollment until 90 days after completion of the study. The data will be requested from CURES between 9/1/2023 to 7/1/2024. As with all study data, this information will only be used for research purposes and will comply with all requirements of the California Confidentiality of Medical Information Act and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

**How long will you be in the study?**

We think you will be in this study for about 90 days.
3. **WHAT ARE THE POSSIBLE RISKS?**

This section describes the possible risks and/or discomforts we anticipate you could experience that are related to the study procedures:

**VR Intervention:**
While using the VR headset, you may experience discomfort with the virtual environment, including temporary headache, vertigo, or nausea. These should be short-term and should stop soon after the headset is removed.

**Fitbit Charge 4 Activity Monitor:**
You may experience minor skin irritation or discomfort from wearing the activity monitor for extended periods of time.

**Surveys:**
It is possible that some of the items in the surveys may make you feel uncomfortable or embarrassed. You are not required to respond to any item that you do not wish to answer. The surveys will be labeled with a unique study number that will link your identity so that only the research team can recognize you.

There are no anticipated long-term risks from participating in this study.

**Risks of sharing data**
Even though we will protect your privacy as much as possible, there is a very small chance that the data could be identified as yours. The risk of this happening is very small, but may increase in the future as technology changes.

Research using data from this study may lead to new tests, drugs, or devices with commercial value. You will not receive any payment for any product developed from research using your samples and data.

If you do not want your data and samples used for other research, you should not participate in this study.

**Follow-up Visit for Discontinuing Participants**
While you are free to discontinue your participation at any time, we encourage you to complete the final study on the 90\textsuperscript{th} day.

4. **ARE THERE BENEFITS IN TAKING PART IN THE STUDY?**

If you agree to take part in this research study, there may or may not be direct medical benefit. The possible benefits of taking part in the research study are pain relief, improved functionality, greater satisfaction with care, and overall improvements in physical and mental health. However, no benefit is guaranteed. It is possible that your condition may remain unchanged or even get worse.

It is possible that none of the programs we are testing will provide benefit. However, you will
continue to receive standard of care treatment from your physician regardless of the group you are assigned to. However, your participation will advance scientific knowledge by helping us evaluate these VR programs.

We hope the information learned from this research study will benefit other individuals with acute or semi-acute pain in the future by helping us to learn how we can reduce pain and improve functionality, while minimizing the use of opioids.

Potential benefits of sharing of data
There is no direct benefit to you from the storage and sharing of your data, but sharing may help researchers learn more about pain management or using VR to help manage other diseases, which may help you or others in the future.

5. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

• The study is stopped or suspended;
• Funding for the study is reduced, stopped or withdrawn;
• If it is in your best interest;
• You do not consent to continue in the study after being told of changes in the research that may affect you;
• You do not follow the study procedures.

You may choose (or you may be required) to withdraw from certain parts of the study, but invited to continue with other parts. For example, you might stop using the audiovisual experience, but continue to fill out the surveys. Separate written consent will be requested if your continued participation will involve procedures not described in this consent form.

6. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

7. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not be used. Organizations that may look at and/or copy your medical records for research oversight, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.
Attached to this consent form is an “Authorization Form” that outlines with whom your information may be shared for the purposes of this research and under what circumstances.

We might share your information and/or research samples collected in this study with other researchers at Cedars-Sinai, other academic institutions, or third-party commercial entities for future research without additional informed consent from you. Information that identifies you will be removed and will not be shared with other researchers or anyone outside of Cedars-Sinai.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

**Protections from Forced Disclosures (Subpoenas) – Certificates of Confidentiality**

To further protect your private identifiable information, we have obtained a Certificate of Confidentiality (Certificate) from the federal government.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law such as child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as including research data in the medical record.
Data Storage and Sharing
Your study data will be stored securely at Cedars-Sinai or at sites NIH selects for this study. Your data will be stored indefinitely. We will do our best to protect your personal information. Your name and other personally-identifying information will not be kept with the data. Your data will either be stored without a code linking them to you or they will have a code that links to your identifying information. If your data has a code, the key to the code will be kept at Cedars- Sinai in a separate, secure area and will not be shared outside of Cedars-Sinai.

This study is part of the NIH HEAL Initiative focused on understanding and developing new treatments for addiction and pain. Research gives us the best information and progresses more quickly when data is available from many studies and many individuals, and when many researchers can work with the data and samples and analyze them in different ways. Therefore, your data will be used for this and other NIH HEAL Initiative studies. Your stored data will also be made widely available to other researchers. The shared data may be used indefinitely for research not related to this study or the HEAL Initiative, without asking you for additional consent.

If you withdraw from this research study before it is done, we will keep and continue to use data and samples that have already been collected.

8. **WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?**

You will not be in danger of any illness or injury from this research study. However, should you believe that you are ill or have been injured as a result of your participation, please contact the study team at the phone number listed on page 1 of this consent form.

9. **FINANCIAL CONSIDERATIONS**

*Costs of Participation*
You and your insurance company will not be charged for your participation in this research study. The Sponsor will cover the cost of all items, drugs and services required by this study, including any procedures required by the study that may be standard of care.

*Compensation for Participating*
You will be eligible for up to $225 in Amazon gift card codes at the end of the study. You will be emailed surveys throughout the course of the study. Each email will have a link to a set of surveys:
- After completing 4 of the 5 sets of surveys (80%) in the 1st month, you will be sent a $25 Amazon gift code.
- After completing 3 of the 4 sets of surveys (75%) of the surveys in the 2nd month, you will be sent another $25 Amazon code.
- Once you complete 8 of the 10 sets of surveys (80%) in the 3rd month and return the equipment, you will be sent a $175 Amazon gift code.

_The $175 Amazon code will not be released until the audiovisual headset and Fitbit device has been returned._
Financial Interest in the Research
The PI and institution have no potential financial conflict of interest with respect to this study.

10. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact the investigator listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, or concerns that you want to discuss with someone who is not associated with this study, or want to offer suggestions or feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP)
Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

11. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;
(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that by consenting to participate in the research, you are not giving up any of your legal rights;
(7) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and
(8) You have been provided with a copy of the “Experimental Subject’s Bill of Rights”, if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and the Experimental Subject’s Bill of Rights.
# Signature Page

## Consent Form for Research

**Signature by the Participant:** I hereby agree to participate in the research study described to me during the informed consent process and described in this informed consent form. **You will be given a signed copy of this form.**

<table>
<thead>
<tr>
<th>Name of Participant (Print)</th>
<th>Signature</th>
<th>Date Signed</th>
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If the participant is aged 13 to 17 years old, a signature from the participant’s parent or guardian is required. Please complete the following if applicable:

**Signature by the Participant’s Parent or Guardian:** I hereby give permission for my child to participate in the research study described to me during the informed consent process and described in this informed consent form.

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<tr>
<th>Parent/Guardian Name (Print)</th>
<th>Signature</th>
<th>Date Signed</th>
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**Signature by the Investigator:** I attest that all the elements of informed consent described in this form have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.

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<tr>
<th>Name of Investigator (Print)</th>
<th>Signature</th>
<th>Date Signed</th>
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APPENDIX: EXPERIMENTAL SUBJECT’S BILL OF RIGHTS

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of any signed and dated written consent form used in relation to the experiment.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject’s decision.
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Pre-screening</th>
<th>Screening Week Day -8 to -2</th>
<th>Day -1 to 0</th>
<th>Day 1 (+6 days)</th>
<th>Day 7 (+6 days)</th>
<th>Day 15 (+6 days)</th>
<th>Day 21 (+6 days)</th>
<th>Day 30 (+6 days)</th>
<th>Day 45 (+6 days)</th>
<th>Day 60 (+6 days)</th>
<th>Day 75 (+6 days)</th>
<th>Day 90 (+6 days)</th>
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<td>Prospective patient identified (DEEP 6 or provider registry)</td>
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<td>Confirm eligibility and Informed Consent via telephone and REDCap</td>
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<td>Online Pain Intensity Journal (7 days)</td>
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<td>Screening Week Online Baseline Survey</td>
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<td>Randomization</td>
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<td>Participant receives study intervention kit</td>
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<td>Technical onboarding call</td>
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<td>Intervention: Participant uses VR therapy program and wears Fitbit Charge 4 watch X</td>
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<td>Online survey: NIH HEAL Minimum Dataset</td>
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<td>Immersive Tendency Questionnaire (ITQ) and Motion Sickness Propensity Survey X</td>
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<td>Treatment expectation question</td>
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<td>Online survey: Primary outcome: PROMIS® Pain Interference</td>
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<td>PROMIS® Physical Function, Anxiety, Depression, Sleep disturbance; Pain intensity/interference with Enjoyment of life/interference with General activity (PEG), PCS-6</td>
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<td>EMR data: Charlson Comorbidity Index, CURES and EMR: Prescription Data</td>
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<td>Perceived study arm question, treatments in the last 90 days question</td>
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<td>Online survey: PHQ-2, GAD-2, PGIC, TAPS (1/2)</td>
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<td>Event Assessment: AE, SAE and UP review and reporting</td>
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ITQ: Immersive Tendency Questionnaire
PEG: Pain, Enjoyment, General Activity
PCS-SF: Pain Catastrophizing Scale-Short Form 6
PHQ-2: Patient Health Questionnaire-2
GAD-2: Generalized Anxiety Disorder 2-item
PGIC: Patient Global Impression of Change
TAPS: Tobacco, Alcohol, Prescription Medication, and Other Substance Use
AE: Adverse event
SAE: Serious adverse event
UP: Unanticipated Problem
AUTHORIZATION FOR USE AND DISCLOSURE OF IDENTIFIABLE HEALTH INFORMATION FOR RESEARCH

1. USE AND DISCLOSURE OF HEALTH INFORMATION

If you agree to this Authorization, you give permission to the Sponsor, Principal Investigator, other investigators and their research team described in the Consent Form for Research (“Research Team”) to use or disclose your identifiable health information (“private information”) for the research study titled “Randomized-controlled trial of virtual reality for chronic low back pain to improve patient-reported outcomes and physical activity” which is described in the Consent Form for Research (“Consent Form”) to which this Authorization is attached. In particular, you authorize the research team acting under the direction of the Principal Investigator to review your medical records and collect your private information from the following sources:

☐ Laboratory tests
☐ Pathology reports
☐ Imaging reports (e.g., x-rays or scans)
☐ Photographs or videos of your image
☒ Doctor/clinic records
☒ Hospital/medical records
☐ Mental health records
☐ Billing records
☐ Other tests or other types of medical information: survey responses, CURES database

2. WHO WILL HAVE ACCESS TO YOUR PRIVATE INFORMATION?

Your private information will be used by and/or shared with the Research Team.

In addition to the research team, if applicable, the following parties may receive your private information and inspect your records:

- The reviewing Institutional Review Boards and Cedars-Sinai offices with authority to oversee research compliance.
- U.S. government agencies, such as the Food and Drug Administration and the Department of Health and Human Services.
- Researchers at other organizations who are participating in this research study.
- The Study Sponsor, its business partners, and Cedars-Sinai’s business partners for matters related to research study oversight, data analysis, use of research results in product development, and payment or reimbursement.
• Representatives from regulatory agencies in other countries may join in the review of your research records, including research-related medical reports and information, with the Sponsor and/or the FDA.

Cedars-Sinai is required by law to protect your private information. However, the recipients described above may re-disclose (or share) your information with other parties unless such sharing is prohibited by law.

3. WHEN WILL MY AUTHORIZATION EXPIRE?

By signing this document, you authorize the use and sharing of your private information until the end of the research study and any related optional sub-study you choose to participate in.

4. REVOKING AUTHORIZATION

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, the research team may still use or disclose private information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to the Principal Investigator of the research study by writing to the Office of Research Compliance and Quality Improvement, 6500 Wilshire Blvd., Suite 1800, Los Angeles, Calif. 90048 and/or emailing to ResearchConcerns@cshs.org.

5. NOTICE OF RIGHTS AND OTHER INFORMATION

You do not have to agree to this Authorization, but if you do not agree, you may not participate in the research study. The Research Team may not condition (withhold or refuse) treating you on whether you agree to this Authorization.

If you agree to this Authorization, please sign on the appropriate signature line below. You will receive a copy of this Authorization.
SIGNATURE PAGE

Authorization for Use and Disclosure of Identifiable Health Information (Research)

Authorization for Use and Disclosure of Identifiable Health Information (Research): I hereby agree that my identifiable health information may be used and/or disclosed in accordance with this “Authorization for Use and Disclosure of Identifiable Health Information (Research)” form.

Name of Participant (Print)  Signature  Date Signed