A Decentralized, Randomized, Controlled Trial of EaseVRx-8w+ for Chronic Low Back Pain

Principal Investigator: Todd Maddox, PhD

Funded by: AppliedVR, Inc.

Protocol Version Number: v.3.0

Protocol Version Date: 14JUL2022

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Section 12.1	Update database lock date	Updated to reflect database lock date in Statistical Analysis Plan
	Update Informed Consent Form Version	Both the initial and most recently revised version of the protocol have the same version number. The revised version will be listed as version 2.0.
	Update Statistical Analysis Plan	Updated to reflect randomization ratio listed on Protocol
	Add Request for Feedback Letter	Added letter to obtain consent from participants to receive testimonials

Table of Contents

1 STATEMENT OF COMPLIANCE

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

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

The protocol, informed consent form(s), and recruitment materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

2 PROTOCOL VERSION HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	02NOV2021	Original protocol	N/A
1.1	02FEB2022	Updated schedule of activities to include PHQ-9 question 9 Changed order of enrollment 2) Removed wording about 1:1:1:1 ratio of randomization 3) Added screenshot of Curebase sign up page 4) Added new demographic message in Communication Plan 5) Added verbiage in communication plan to confirm that participants have received their VR headset 6) Added option for participants to receive text notifications during the study in pre-screen survey 7) Added Pretreatment Survey Completion screen 8) Updated Support Protocol & Scripts	Ensures screening process is reflected in the SoA Moving the shipment survey before the pre-treatment BPIs allows for simpler CSV data output 2) Randomization ratio is 2:1:2:1 on protocol 3) This is the account creation page for Curebase 4) Allows us to confirm if the participant has received the headset and confirms the start of the intervention 5) Ensures we receive demographic information from patients if they leave the website 6) All study notifications will be sent via email due to complexity of study and text message character limit. To reduce the number of notifications sent, participants will have the option to receive texts 7) Positive reinforcement for participants to complete pretreatment surveys 8) Updated questions and answers to reflect flow of study

2.0	04MAR2022	(1) Change randomization ratio to 1:1:1:1 (2) Updated name of PI from Laura Garcia to Todd Maddox (3) Added new Study Investigator Charisse Sparks, M.D. (4) Updated the number of participants the study will enroll from 800 participants to 1000 (5) Add exclusion criteria: only one participant per household allowed to participate (6) Add exclusion criteria: recent or future medical procedures (7) Clarify language for payment schedule	(1) Upon further investigation, we determined that a randomization of 1:1:1:1 would better suit the study and would help us reach the outcomes we want to achieve. It also allows for easier recruitment of participants and randomization through Curebase. (2) PI Laura Garcia is no longer part of AppliedVR (3) Charisse Sparks is the new CMO for AppliedVR and will now be involved in the study monitoring (4) The increase in number of participants that will enroll is necessary due to the new change in randomization ratio (5) Protects integrity of study so that study details are not shared between household members (6) To adjudicate acute versus chronic pain. We are studying chronic pain therefore it is necessary to exclude acute pain diagnosis (7) Provide clarification that payment is tied to survey completion and not VR session completion

3 PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Title: A Decentralized, Randomized, Controlled Trial of EaseVRx-8w+ for Chronic Low Back Pain

Protocol Version/Date: v.1.0 / 02NOV2021

This protocol has been read and approved by:

SPONSOR:

Josh Sackman *President and co-Founder* *AppliedVR, Inc.*	Date

CRO:

Iman Ahmad *Sr. Director, Clinical Affairs* *MCRA, LLC*	Date

4 SIGNATURE PAGE

I have read and understand this protocol and will conduct the study in accordance with this protocol, all attachments and amendments, applicable Food and Drug Administration regulations, HIPAA, IRB requirements, and the policies of the institutions where the study will take place.

In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing AppliedVR, Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

Protocol Title: A Decentralized, Randomized, Controlled Trial of EaseVRx-8w+ for Chronic Low Back Pain

Protocol Version/Date: v.1.0 / 02NOV2021

Principal Investigator:

Todd Maddox, PhD
(Print Name)

(Signature) (Date)

5 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
AVR	AppliedVR, Inc.
BPI	Brief Pain Inventory
CAP-6	Concerns About Pain
CBT	Cognitive Behavioral Therapy
CDC	Center For Disease Control and Prevention
CDRH	FDA Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CID	Clinically Important Difference
CLBP	Chronic Low Back Pain
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Sars-cov-2 Coronavirus
CRF	Case Reporting Form
FDA	Food And Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IDE	Investigational Device Exemption
IRB	Institutional Review Board
JMIR	Journal Of Medical Internet Research
MCRA	Company Name: Regulatory Consultants
MHLC-C	Multidimensional Health Locus of Control
ODI-2.1b	Oswestry Disability Index
OUD	Opioid Use Disorder
PGIC	Patient Global Impression of Change
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire (9 Question Instrument)
PI	Principal Investigator
PMID	PubMed Identification
PROMIS	Patient-Reported Outcomes Measurement Information System
PSEQ-10	Pain Self-Efficacy Questionnaire (10 Question Instrument)
PUI	Perceptual User Interface
RCT	Randomized Controlled Trial
ROM	Read Only Memory
SAE	Serious Adverse Event
SUS	System Usability Scale
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
USA	United States of America
VR	Virtual Reality

6 PROTOCOL SUMMARY

6.1 Synopsis

Title:	A Decentralized, Randomized, Controlled Trial of EaseVRx-8w+ for Chronic Low Back Pain
Study Sponsor	**AppliedVR, Inc.** 16760 Stagg Street, Unit 216 Van Nuys, CA 91406 Phone: 1-844-204-9093
Study Investigators	**Todd Maddox**, PhD (Principal Investigator) Charisse Sparks, MD Liesl Oldstone, PhD Beth Darnall, PhD
Investigational Device	EaseVRx is a prescription-use immersive virtual reality system intended to provide a combination of biopsychosocial pain education, diaphragmatic breathing training, relaxation exercises, and executive function games for participants diagnosed with chronic low back pain (CLBP). The device is intended for in-home use for the reduction of pain and pain interference associated with CLBP.
Study Purpose	The aim of this randomized controlled trial (RCT) is to assess outcomes for virtual reality therapy (including pain intensity, pain interference, anxiety, depression, physical function, sleep, behavioral skills development, health outcomes and satisfaction) along with healthcare utilization and costs in participants with CLBP.

Study Design	This is a decentralized, randomized controlled trial with four parallel study arms comparing change from pre-treatment to end-of-treatment to 12-months post-treatment in the EaseVRx-8w, EaseVRx-8w plus extended on-demand and Control groups. After consenting to join the study, participants will be randomized and allocated to one of four treatment programs. Study devices will be delivered to the participant's home with instructions for use via FedEx with complementary remote technical support. • participants in the EaseVRx-8w arm will participate in an 8-week interventional program and continue to be followed for 24 months after completion of treatment • participants in the EaseVRx-8w plus extended on-demand arm will enroll in an 8-week interventional program and be offered an extended 8-week on-demand period, and continue to be followed for 24 months after the completion of treatment • participants in the first control arm will receive 2D Sham VR virtual reality content during the 8-week interventional program and continue to be followed for 24 months after the completion of treatment • participants in the second control arm will receive 2D Sham VR virtual reality content during the 8-week interventional program and be offered an extended 8-week on-demand period, after which they will continue to be followed for 24 months after the completion of treatment All trial participants will be monitored for pain intensity and pain interference, physical function, behavioral skills development, health outcomes and satisfaction. Additionally, to assess resource use associated with CLBP, participant data will be run through a secure Datavant matching process to be linked to their healthcare claims data if it is available in the Komodo data set. The claims will provide descriptive characterizations of resource use and healthcare costs associated with CLBP. For participant-level changes in resource use, and for comparisons between study arms, only the participants with complete claims files will be assessed. Claims-matched data will capture all interactions with the healthcare system that generate an insurance claim record, which includes such things as physician visits, interventions such as steroid injections, surgery or physical therapy, emergent use of services, medications, and diagnostic procedures. Claims adjudication often lags a few months, so the most robust analyses of utilization will be performed about 6 months after the time point of interest. Health economic modeling will be performed after 1 year to assess the cost and economic outcomes of the EaseVRx intervention.

	The Komodo claims data provides a real-world source of utilization and cost parameters associated with claims of CLBP. As such, it can be used more broadly to either compare the study participants' resource use and costs to the broader population of participants with CLBP, or a "synthetic arm" can be constructed using available demographic data to match any of the study arms.
Study Duration	This study is expected to take approximately 36 months for completion.
Number of Participants & Sites	This study will enroll approximately 1000 participants using a fully decentralized direct-to-participant trial design without any central data collection sites.
Randomization Scheme	Enrolled participants will be randomized 1:1:1:1 and assigned to one of four treatment arms: • 56-day skills-based VR program (EaseVRx-8w) • 56-day skills-based VR program followed by an extended 56-day on-demand period (EaseVRx-8w plus extended on-demand) • 56-day control (Sham VR) • 56-day control followed by an extended 56-day on-demand period (Sham VR plus 8w extended on-demand)
Evaluation Schedule	Participants in all 4 treatment arms will be evaluated at the following timepoints: pre-treatment, 2x/week during treatment, immediately post-treatment (day 56 in all arms), 4-weeks post-treatment, 8-weeks post-treatment, 12-weeks post-treatment, 6 months post-treatment, 12 months post-treatment, 18 months post-treatment, 24 months post-treatment.
Intended Participant Population	Mixed community-based sample and physician-referred sample of individuals aged 18 and older with a diagnosis of CLBP (defined as moderate to severe pain lasting longer than three months). Participant recruitment methods will aim to guarantee data collection from the following groups: • At least 250 of the approximately 1000 recruited participants will be ≥ 65+ years old. • At least 250 of the approximately 1000 recruited participants will be of lower education and socioeconomic status (based on education level, employment status and annual household income).
Enrollment Target	Approximately 1000 participants

Inclusion Criteria	In order to be eligible to participate in this study, participants must meet all of the following criteria: 1. Male and female adults aged 18-85. 2. Self-reported chronic low back pain that will be confirmed with claims data when available. 3. Pain duration of at least three months. 4. Average pain intensity score of ≥ 4 and average pain interference score of ≥ 4 on the 0-10 Brief Pain Inventory (BPI) Pain Scale for the past month at screening. 5. Fluency in English. 6. Willing and able to comply with all study procedures including all required restrictions for the duration of study participation. 7. Able to give voluntary, written informed consent to participate and have signed an Informed Consent Form specific to this study. 8. Access to Internet for the duration of their study participation (24 months). 9. Access to a smartphone or computer for the duration of the study. 10. Availability of a physical mailing address that is not a PO box address for receipt of the device. 11. Completed the Baseline Survey plus at least two of the five sets of participant surveys that are administered during the 10-day pretreatment assessment period. 12. Able to provide photo ID.

Exclusion Criteria	Participants who meet any of the following criteria will be excluded from participating in this study: 1. Unable to understand the goals of the study due to cognitive difficulty. 2. Any medical condition that may prevent the use of virtual reality (e.g., current, or prior diagnosis of epilepsy, seizure disorder, hypersensitivity to flashing light or motion, migraines, any medical condition predisposing participant to nausea or dizziness, dementia, absence of stereoscopic vision or severe hearing impairment). 3. Injury to eyes, face, or neck that prevents comfortable use of VR. 4. Index back pain is linked to a cancer-related diagnosis. 5. Possible suicidal ideation as indicated by the 9th item of the Participant Health Questionnaire-9 (PHQ-9). 6. Previous participation in the 2020 AVR EaseVRx pivotal study. 7. Receiving worker's compensation and/or involved in any active litigation related to an injury. 8. Current or recent participation (i.e., within the last 2 months) in any other research study involving a drug, device, vaccine, or other interventional treatment product; or plans to participate in another research study over the next 24 months. 9. Participation of two or more members in one household 10. Recent or future medical procedures scheduled related to any current diagnosis
Primary Objective	The primary objective of this study is to evaluate the following: **Primary Endpoint:** Assess the impact of skill-based VR on pain Intensity or Interference compared to sham VR. • Assess the effect of EaseVRx vs. Sham VR on group score change from baseline to end of treatment on pain intensity • Assess the effect of EaseVRx vs. Sham VR on group score change from baseline to end of treatment on pain interference

Secondary Objectives	The secondary objectives of this study include the following: 1. Assess the effect of EaseVRx vs. Sham VR by comparing: • Percentage of participants with a ≥ 30% change in pain intensity measured with the Brief Pain Inventory (BPI) from pre-treatment to end-of-treatment (8 weeks) for each group • Percentage of participants with a ≥ 30% change in pain interference measured with the BPI (as represented by a single composite score derived from 7 pain interference questions) from pre-treatment to end-of-treatment (8 weeks) for each group 2. Assess the effect of EaseVRx vs. Sham VR by comparing: • Change in Oswestry Disability Index (ODI-2.1b), PROMIS Sleep Disturbance, PROMIS Depression and PROMIS Anxiety from pre-treatment to end-of-treatment (8 weeks) for each group 3. Assess effect of EaseVRx vs. Sham VR by comparing participant satisfaction at end-of-treatment (8 weeks) for each group
Exploratory Objectives	The exploratory objectives of this study include the following: 1. Assess the impact of skill-based VR in follow-up pain adjusting for baseline pain. 2. Assess the impact of skill-based VR based on clinical importance changes in a responder framework. This endpoint is included to provide sensitivity around the secondary endpoint. 3. Assess the impact of skill-based VR on changes in healthcare utilization and outcomes throughout an 8-week intervention and follow-up period. 4. Assess effect of EaseVRx vs. Sham VR by comparing change in Concerns About Pain (CAP-6); and behavioral skills from pre-treatment to end-of-treatment for each group. 5. Assess effect of EaseVRx vs. Sham VR by comparing participant Global Impression of Change (PGIC) and system usability (as measured with the System Usability Scale; SUS) at end-of-treatment for each group. 6. Assess effect of EaseVRx vs. Sham VR by comparing change in all objectives from pre-treatment to end-of-treatment, 4 weeks post treatment, 8 weeks post treatment, 12 weeks post treatment, 6 months post treatment, 12 months post treatment, 18 months post treatment and 24 months post treatment in the EaseVRx-8w and EaseVRx-8w plus extended on-demand groups.
Clinical Research Organization (CRO)	**MCRA, LLC** 803 7th Street NW Washington DC 20001

Virtual Trial Platform	**Curebase Inc.** 340 S Lemon Ave #3356 Walnut, CA 91789 United States

6.2 Schedule of Activities (SoA)

VISITS	Pre-Treatment		Treatment		Post-Treatment (PT)						
	Day -10[1]	Day -9 to 0	Wks. 1-8	Day 56	4 Wks. (84 +7 days)[1]	8 Wks. (112 +7 days)[1]	12 wks. (140 +7 days)[1]	6 months (238 +30 days)[1]	12 months (420 +30 days)[1]	18 months (602 +30 days)[1]	24 months (784 +30 days)[1]
Pre-Screener	X										
Suicidality Screener - 9th item of PHQ-9	X										
Demographic survey	X										
Informed Consent via Curebase	X										
Identity Verification	X										
Brief Pain Inventory (BPI) pain intensity/interference	X	X[2]	X[3]	X	X	X	X	X	X	X	X
Oswestry Disability Index	X			X	X	X	X	X	X	X	X
PROMIS Sleep Disturbance	X			X	X	X	X	X	X	X	X
PROMIS Depression	X			X	X	X	X	X	X	X	X
PROMIS Anxiety	X			X	X	X	X	X	X	X	X
Concerns About Pain (CAP-6) Scale	X			X	X	X	X	X	X	X	X
Behavioral Skills Use	X			X	X	X	X	X	X	X	X
Participant's Global Impression of Change Scale (PGIC)				X	X	X	X	X	X	X	X
Pain Self-Efficacy Questionnaire (PSEQ-10)	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Multidimensional Assessment of Interoceptive Awareness (Ver 2)	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Multidimensional Health Locus of Control	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
VR Sickness Questionnaire			X[4]	X[4]	X[4]	X[4]					
participant Satisfaction				X							
System Usability Scale (SUS)				X							
Benefits Screening									X		
Shipping Address Survey		X									
EaseVRx User Experience Questionnaire				X		X[5]					
Randomization (performed within Curebase portal)		X									
Ship Intervention kit to participants		X									
Technical onboarding		X									
Record VR compliance/use data[6]			X	X	X[5]	X[5]					
Collect study intervention kit							X				
Perceived Treatment Assignment				X							
Healthcare utilization data analysis				X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]

[1] OPTIONAL survey offered next day.
[2] Two out of five BPI survey instances to be completed over 9-day pre-intervention period.
[3] Research staff will monitor participants' progress through twice weekly BPI surveys.
[4] VR Sickness Questionnaire will be administered once per week during treatment and once per week for the 16-week arms.
[5] For participants assigned to extended 56-day on-demand period only.
[6] Device use to be monitored on a weekly basis when participants connect the device to Wi-Fi. For participants who do not connect their headset to Wi-Fi, compliance will be assessed post-intervention when the headset has been returned.
[7] Komodo data analysis to begin after all participants have completed Day 56 and will be ongoing through 24-month post-treatment visit.

7 INTRODUCTION

7.1 Study Rationale

The aim of this randomized controlled trial (RCT) is to assess the impact of using virtual reality therapy in pain management outcomes – including pain intensity and pain interference levels, back pain function, sleep disturbance, anxiety, depression, behavioral skills development, health outcomes and satisfaction in a cohort of participants with chronic pain of the lower back.

7.2 Background

Chronic pain is one of the most common reasons adults seek medical care[1]: chronic pain affects between 50 and 116 million Americans, more so than cancer, diabetes, and cardiovascular disease combined[1-4]. Other estimates suggest that up to 40% of American adults suffer from chronic pain, ranging from mild to severe[5]. Pain treatment and management are traditionally based around utilizing pharmacological management tools, which typically involve opioids. Although some non-opioid pharmaceuticals and non-pharmacological therapies are becoming available, there is still a significant unmet need for integrative, easily accessible, non-opioid solutions for chronic pain.

Approximately 25 million American adults are living with moderate to severe chronic pain (i.e., pain scoring 4-7 on a Visual Analog Scale and lasting over 3 months) that limits their activities and diminishes their quality of life[6, 7]. Close to 85% of these participants do not find meaningful relief from current non-opioid treatments (i.e., they do not experience a long-term ≥ 50% reduction in their pain levels)[8].

Opioids are commonly prescribed for pain treatment and management. These agents can yield both inconsistent and sub-optimal results[9] and greatly increase the risk of the participant developing an opioid addiction or Opioid Use Disorder (OUD). Data from the U.S. Centers for Disease Control (CDC) revealed that even a single day of opioid therapy can predict up to a 6% increase in the risk of the participant developing a dependency within a year[10].

To reduce addiction and provide relief for the millions of chronic pain sufferers, new low-risk, non-opioid pain analgesics are needed. On-demand digital therapeutics may provide home-based access to pain education and skills-based pain self-management. Particularly during the COVID-19 pandemic, home-based behavioral pain care has gained interest, importance, and engagement among participants. Home-based digital pain treatment options include those involving therapist instruction, as well as fully automated behavioral programs. For the latter, the portfolio of self-treatment options includes computer applications for symptom tracking, education, and treatment; web-based programs that include self-paced multisession skills-based pain management learning modules; and virtual reality (VR) immersive treatment[11].

7.3 Device Description

7.3.1 Indications for Use

EaseVRx is an investigational, prescription-use immersive virtual reality system intended to provide adjunctive treatment based on cognitive behavioral therapy skills and other evidence-based behavioral methods for participants (age 18 and older) with a diagnosis of chronic lower back-pain (defined as moderate to severe pain lasting longer than three months). The device is intended for in-home use for the reduction of pain and pain interference associated with chronic lower back pain.

7.3.2 System Description and Components

EaseVRx is an investigational medical device with preloaded software content on a proprietary hardware platform that delivers cognitive behavioral skills training and other behavioral methods to participants diagnosed with chronic pain. It is an immersive VR system that delivers the VR content while incorporating biopsychosocial pain education, diaphragmatic breathing training, mindfulness exercises, relaxation exercises, and executive functioning games. The medical device integrates an all-in-one head-mounted display with a Software Application and a Breathing Amplifier™ to enable the diaphragmatic breathing exercises. The device is intended to be self-administered, unsupervised in the participant's home while the participant is in a seated position. The device is powered by a rechargeable lithium battery. Each device is intended for a single participant. The medical device is meant for repeated use.

There are two main components of the EaseVRx system, as follows.

Head-Mounted Display (HMD)

The all-in-one mounted display consists of an off-the-shelf VR headset, modified with a Breathing Amplifier™ accessory (See Figure 1 below). The headset is a standalone VR system comprised of the following:

- Adjustable straps to allow the user to comfortably use the headset
- Mounted high resolution display
- Positional audio speaker system
- Buttons to power on/off, control volume, and navigate content
- Integrated microphone for use with some content
- Breathing Amplifier™ modification to direct breath toward microphone

A Breathing Amplifier™ is added to the headset by the Sponsor, AppliedVR, Inc., hereafter AppliedVR. This mechanical attachment is designed to enhance the user's engagement in certain content by amplifying the user's exhalation into the on-board microphone input to generate a visualization of the user's breath within the VR content.

Front View

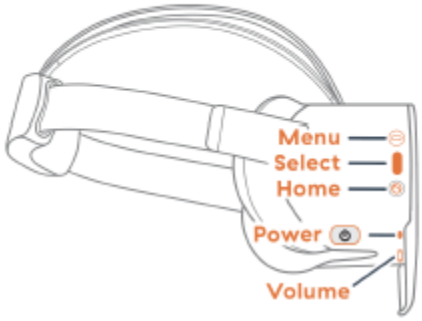

Figure 1: (Left): EaseVRx Headset	(Right): Drawing depicting buttons and their locations

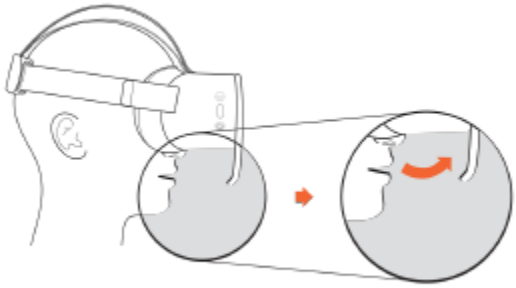

Figure 2: Breathing Amplifier™ Component of EaseVRx

Head-Mounted Display (HMD) Off-the-shelf Software

HMD off-the-shelf software comprises of the following:

- **General operating system:** off-the-shelf operating system modified by AppliedVR to support and execute the functions of EaseVRx
- **Bootloader:** off-the-shelf firmware component that turns on the HMD and verifies that critical software components for operation are present and activated
- **Perceptual User Interface (PUI):** off-the-shelf component that acts as a user interface "wrapper" around the general operating system
- **System ROM:** off-the-shelf general computing component that contains the necessary software and firmware for the device image, and drivers to handle HMD specific functions such as buttons, light sensors, and lens display

7.3.3 AppliedVR Software for EaseVRx

The EaseVRx software is designed to provide cognitive behavioral therapy (CBT) and other behavioral methods within an immersive VR environment. EaseVRx software is installed on a general operating HMD system. The breathing shield component of EaseVRx acts as a mechanical amplifier enabling the software to visualize the exhalation.

EaseVRx runs on an off-the shelf general computing operating system, Android, that was modified by AppliedVR to support EaseVRx's delivery of cognitive behavioral therapy, hereby referred to as "content." Users receive EaseVRx pre-installed with all necessary content. EaseVRx does not require any participant information in order to initiate treatment, nor is there anything for a participant to install. Upon receiving the device, a participant only needs to power the device on and follow the instructions on the display to initiate sessions.

7.4 Study Interventions

The study intervention will include evidence-based digital devices that offer non- pharmacological solutions to managing pain.

Skills-Based VR (EaseVRx)

Participants allocated to the two EaseVRx arms will use a multi-modal, skills-based, self-management VR program, called EaseVRx (AppliedVR; Los Angeles, CA), that incorporates the evidence-based principles of CBT and mindful meditation. EaseVRx combines biopsychosocial education, pain education, breathing training, relaxation exercises, and executive functioning games to provide a mind-body approach toward living better with chronic pain. The standardized, reproducible, 56-day program delivers a combination of skills training and CBT-related treatments through scheduled daily virtual experiences. Each VR experience lasts between 2-16 minutes, with an average duration of 6 minutes. The VR treatment modules are designed to minimize triggers of emotional distress or cybersickness. For the proposed study, participants in the skills-based VR arm will be instructed to complete the full 56-day treatment using a Pico G2 4K VR headset. There are 5 types of modules, as follows:

- **Interoceptive modules:** an entirely new and powerful element added to the treatment program to help understand and perceive what is going on inside the body, and to provide a biofeedback-like platform in which the changes in the observed environment reflect a progressively enhanced state of relaxation.
- **Education modules**: helps the user understand why the VR exercises are relevant to their pain as well as specific topics often used in pain psychology treatments. They learn about the neurobiology of pain, the role of mood and stress in pain, pain catastrophizing, activity pacing and goal setting. The goal is for the user to create self-management steps and a toolkit of strategies they can use to manage their response to pain.
- **360-degree video modules:** high quality 360-degree videos with voiceovers, music, breathing effects, and sound effects are designed to maximize relaxation and engagement of participants.
- **Game modules:** games are designed to maximize distraction and engagement, increasing the cognitive load on participants, and decreasing their perception of pain.

- **Dynamic breathing modules:** based on evidence-based biofeedback training designed to enhance awareness of one's physiological response to pain and to self-regulate that response. In a virtual world, the user experiences a gamified biofeedback session where they are introduced to awareness of their breath via visualization in the virtual environment in the form of air bubbles. In multiple sessions, the user receives increasingly challenging tasks to practice diaphragmatic breathing while interacting with the virtual environment. The user is also asked to pace their breath according to an expanding and contracting ring in the environment to slow their breath and create physiological changes associated with relaxation. The user's exhale is measured by the microphone embedded in the Pico G2 hardware, offering biodata-enabled immersive therapeutics.

Sham VR

In an ongoing systematic literature review using Cochrane criteria, few VR studies have been found that adequately blind participants to the treatment procedure. VR-CORE guidelines suggest using an active control in VR clinical trials and promote the use of non-immersive, 2D content within a VR headset as an optimal control. Thus, participants in the Sham VR group will receive the same Pico G2 4K headset as participants in the immersive VR groups, but rather than view 360-degree, 3D, interactive content specially selected for efficacy, they will only have access to 2D nature footage with neutral music layered on top that is selected to be neither overly relaxing nor distracting. The experience of Sham VR is similar to watching a large-screen TV, but it is not interactive. The advantage of Sham VR is that it controls for the novelty and immersion of the hardware and isolates the effect of VR skill-based training.

7.5 Dosing and Administration

Weeks 1-8:

All participants will receive a VR headset and will be instructed to use VR once a day for 8 weeks.

Weeks 9-16:

For the 2 groups that are assigned to the arms with an extended 56-day on-demand period, participants will have the option of accessing VR for an additional 8-week period at their discretion. These groups will be instructed to use VR on an as-needed basis (i.e., there will be no set requirement for daily use as with the initial 8-week treatment phase).

7.6 Technical Support

Participants in both arms will receive remote technical support from the research and operations team. The idea is that issuing devices is usually insufficient to achieve behavior change; supporting those devices with high-touch yet scalable care is a vital component.

Participants will be provided with device use instructions as well as emails describing the study details. Instructional videos will be made available to participants, and access to remote technical support will be provided.

Participants will receive a telephone number, email, and will have access to contact support staff as needed. The Research support staff will also reach out if there is a lack of survey completion.

7.7 Risk/Benefit Assessment

7.7.1 Known Potential Risks

Short-term risks associated with the study may include minor psychological distress from questionnaires regarding health, and small risk of VR-related "cybersickness," which involves transient symptoms related to entering VR environments (vertigo, nausea, headache). Risks for cybersickness are mitigated by the design of the VR programs in this study. Previous research with this program demonstrates that less than 10% of participants reported cybersickness that prevented them from using Virtual Reality 11, [12]. There are no anticipated long-term risks from participating in this study.

7.7.2 Known Potential Benefits

Potential immediate benefits include reduction of pain due to chronic low back pain (CLBP) and global improvements in psychological health. Potential long-term benefits include improved functionality, development of behavioral coping skills, reduced opioid use, and improved global physical health.

7.7.3 Assessment of Potential Risks and Benefits

Virtual reality hardware and software have advanced significantly in the past several years and sophisticated motion tracking helps to minimize discomfort among participants. Modern studies utilizing VR have found high satisfaction with devices among participants. Participation in the study may alleviate pain among individuals who have previously relied on opioids, subsequently decreasing both opioid-induced side effects and providing pain relief. Sustained pain relief may allow individuals to return to work faster, improve physical mobility, and enhance biopsychosocial health. We believe the short- and long-term anticipated benefits outweigh minimal short-term risks. Furthermore, risks of cybersickness and discomfort will be assessed following 1 week of usage and will be monitored closely.

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

8 STUDY OBJECTIVES AND ENDPOINTS

Aims/Objectives	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
PRIMARY AIM		
Primary Endpoint: Assess the impact of skill-based VR on pain Intensity or Interference compared to sham VR. • Assess effect of EaseVRx vs. Sham VR on group	The primary endpoint in this study is a significant change in pain intensity or pain inference at the end of the 8-week treatment period among individuals in the two skills-based VR arms compared	The Brief Pain Inventory (BPI) survey is a validated instrument with excellent content validity, construct validity, and reliability in participants with chronic pain.

score change from baseline to end of treatment on pain intensity • Assess effect of EaseVRx vs. Sham VR on group score change from baseline to end of treatment on pain interference	to those in the two Sham VR arms. The outcome measure used to quantify this endpoint is the BPI survey. Interference and intensity are tested separately, and therefore, two (2) multiplicity adjusted statistics are produced. Study success will be declared if statistical significance is demonstrated on at least one of the endpoints. The primary endpoint will pool the two EaseVRx stratum (EaseVRx) together and the two Sham stratum (Sham VR) together. The outcome measure is administered before the 8-week intervention, during and immediately upon completion of the 8-week intervention via the Curebase dashboard.	Widely used and therefore may be expected by some reviewers.
SECONDARY AIMS		
Secondary Aim #1: Assess effect of EaseVRx vs. Sham VR by comparing: • Percentage of participants with a ≥30% change in pain intensity measured with the BPI from pre-treatment to end-of-treatment (8 weeks) for each group • Percentage of participants with a ≥30% change in pain interference measured with the BPI (as represented by a single composite score derived from 7 pain interference questions) from pre-treatment to	The first secondary endpoint is the group level comparison of the percentage of participants in each arm that experience a clinically significant change in pain intensity or pain interference respectively. The outcome measure used to quantify this endpoint is the BPI survey. Clinical significance for this endpoint is defined as a 30% change from baseline. Interference and Intensity are tested separately, and therefore, two (2) multiplicity adjusted statistics are produced. Study success will be declared if statistical significance is	The BPI survey is a validated instrument with excellent content validity, construct validity, and reliability in participants with chronic pain. The study is powered to accomplish secondary endpoints which require statistical power beyond what is required for the primary endpoint alone. Therefore, the trial may demonstrate a difference between groups that is small and not necessarily meaningful. The secondary endpoint using this responder definition will accompany the primary results to help interpret the primary results.

end-of-treatment (8 weeks) for each group	demonstrated on at least one of the endpoints. The outcome measure is administered before the intervention, during and immediately upon completion of the 8-week intervention via the Curebase dashboard.	See the Statistical Analysis Plan for additional details.
Secondary Aim #2: Assess the effect of EaseVRx vs. Sham VR by comparing: • Change in Oswestry Disability Index (ODI-2.1b), PROMIS Sleep Disturbance, PROMIS Depression and PROMIS Anxiety from pre-treatment to end-of-treatment (8 weeks) for each group	The secondary endpoints are clinically significant changes in Oswestry Disability Index (ODI-2.1b) results, PROMIS Sleep Disturbance scores, PROMIS Depression scores and PROMIS Anxiety scores from pre-treatment to end-of-treatment (8 weeks) for each group. Outcome measures used for this endpoint include the BPI survey, Oswestry Disability Index (ODI-2.1b) results, PROMIS Sleep Disturbance scores, PROMIS Depression scores and PROMIS Anxiety scores. The outcome measures are administered before the intervention and immediately upon completion of the 8-week intervention via the Curebase dashboard.	The ODI, and PROMIS Sleep Disturbance, Depression and Anxiety surveys are all validated instruments with excellent content validity, construct validity, and reliability in participants with chronic pain.
Secondary Aim #3: Assess effect of EaseVRx vs. Sham VR by comparing participant satisfaction at end-of-treatment (8 weeks) for each group.	The third secondary endpoint compares participant satisfaction at the end of treatment across the EaseVRx and Sham groups. The outcome measure used to quantify this endpoint is a custom survey developed by the AVR research team to assess participant satisfaction. This outcome will be collected immediately upon completion	The AVR participant Satisfaction survey was developed internally by the Research team to assess satisfaction with the EaseVRx and Sham treatments.

	of the 8-week intervention via the Curebase dashboard.	
EXPLORATORY AIMS		
Exploratory Aim #1: Assess the impact of skill-based VR in follow-up pain adjusting for baseline pain. This endpoint is included to primary sensitivity around the primary endpoint.	Continuous group difference in follow-up scores adjusted for baseline. Interference and Intensity are tested separately, and therefore, two (2) multiplicity adjusted statistics are produced. The outcome measure used to quantify this endpoint is the BPI survey.	Included to enable understanding potential limitations in the primary endpoint. The variables are inclusion criterion, and therefore regression to the mean could be important. Deals with floor and ceiling effects of the change score. Does not require the pre- and post-values to be linearly related.
Exploratory Aim #2: Assess the impact of skill-based VR based on clinical importance changes in a responder framework. This endpoint is included to provide sensitivity around the secondary endpoint.	Clinically Important Difference (CID) in Interference/Severity Brief Pain Interference Scale (score range 0-10); CID = 2 Brief Severity Item (score range 0-10); CID = 2 Interference and Intensity are tested separately, and therefore, two (2) multiplicity adjusted statistics are produced.	Commonly CID thresholds are commonly used to answer the question of whether statistically significant differences in groups are driven by meaningful improvements for individuals. Both 30% change and CID thresholds are used in responder analyses. By including both, the research team will answer the question of whether the study would have obtained a different result using one versus the other. See the Statistical Analysis Plan for additional details.
Exploratory Aim #3: Assess the impact of skill-based VR on changes in healthcare utilization and outcomes throughout an 8-week intervention and follow-up period.	Pain-related healthcare utilization will be assessed in a subset of participants for whom access to complete insurance claims files are available. All claims for medical care associated with CLBP will be included and includes claims for the following types of services:	While the EaseVRx intervention targets pain and pain interference, it should follow that pain-related medical resource use should be reduced with clinical improvement. Healthcare resource use is difficult to track and assign to a particular diagnosis. Linking the participants to their own claim

	• Number and type of imaging and diagnostic procedures • Number and type of health care practitioner visits including specialty care • Number of chiropractic and physical therapy visits • Number and type of emergency room visits • Number and type of surgeries • Number, type, and duration of hospitalizations • Frequency of 30-, 60-, 90-day readmissions • Complications that can be assigned to the pain or pain-related interventions	records to allow for assessment of changes over time.
Exploratory Aim #4: Assess effect of EaseVRx vs. Sham VR by comparing change in participant's Global Impression of Change (PGIC), Concerns About Pain (CAP-6); and behavioral skills from pre-treatment to end-of-treatment for each group.	The exploratory endpoints are clinically significant changes in PGIC, CAP and behavioral skills from pre-treatment to end-of-treatment (8 weeks) for each group. Outcome measures for this endpoint include the PGIC, CAP-6 and a behavioral skills survey developed by the AVR team.	The CAP-6 survey is a validated instrument with excellent content validity, construct validity, and reliability. The behavioral skills survey has not been validated but has been found informative for internal use.
Exploratory Aim #5: Assess effect of EaseVRx vs. Sham VR by comparing participant Global Impression of Change (PGIC) and system usability (as measured with the System Usability Scale; SUS) at end-of-treatment for each group.	The exploratory endpoint compares PGIC and SUS at the end of treatment across the EaseVRx and Sham groups. The outcome measure used to quantify this endpoint is the PGIC and SUS survey.	The PGIC and SUS surveys are validated instruments with excellent content validity, construct validity, and reliability.
Exploratory Aim #6: Assess effect of EaseVRx vs. Sham VR by comparing change in all objectives from pre-treatment to end-of-treatment, 4 weeks	See descriptions above	See descriptions above

post treatment, 8 weeks post treatment, 12 weeks post treatment, 6 months post treatment, 12 months post treatment, 18 months post treatment and 24 months post treatment in the EaseVRx-8w and EaseVRx-8w plus extended on-demand groups.		

9 STUDY DESIGN

9.1 Overall Design

This RCT will enroll approximately 1000 participants with a self-reported diagnosis of chronic lower back pain (defined as moderate to severe pain lasting longer than three months) to test the efficacy of skills-based VR (EaseVRx) on long term pain management as an adjunct to traditional medical therapy. Enrolled participants will be randomized 1:1:1:1 and assigned to one of four treatment arms:

- 56-day skills-based VR program (EaseVRx-8w)
- 56-day skills-based VR program followed by an extended 56-day on-demand period (EaseVRx-8w plus extended on-demand)
- 56-day control (Sham VR-8w)
- 56-day control followed by an extended 56-day on-demand period (Sham VR-8w extended on-demand)

The primary outcome will be assessed using the BPI: an eight-item scale assessing pain intensity and pain interference on general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Each participant's BPI score will be assessed immediately before the intervention, during the intervention, immediately following the intervention, and at 4-, 8-, 12-weeks, and 6-, 12-, 18-, and 24-months post intervention (see Schedule of Activities in Section 5.2).

Secondary outcomes include the Oswestry Disability Index score (ODI v2.1b), PROMIS Sleep Disturbance, PROMIS Depression, and PROMIS Anxiety that will be evaluated before the intervention, immediately following the intervention (Day 56 in all arms), 4-weeks post-treatment, 8-weeks post-treatment, 12-weeks post-treatment, 6 months post-treatment, 12 months post-treatment, 18 months post-treatment, and 24 months post-treatment. participant Satisfaction will be evaluated at Day 56.

Additionally, participants will be administered the following surveys as tertiary and exploratory outcomes at the specified timepoints:

- Participant's Global Impression of Change Scale (PGIC): Day 56, 4-weeks post-treatment, 8-weeks post-treatment, 12-weeks post-treatment, 6 months post-treatment, 12 months post-treatment, 18 months post-treatment, and 24 months post-treatment

- Concerns About Pain (CAP-6) Scale: Baseline, Day 56, 4-weeks post-treatment, 8-weeks post-treatment, 12-weeks post-treatment, 6 months post-treatment, 12 months post-treatment, 18 months post-treatment, and 24 months post-treatment
- Systems Usability Scale (SUS): Day 56
- Behavioral Skills Use: Baseline, Day 56, 4-weeks post-treatment, 8-weeks post-treatment, 12-weeks post-treatment, 6 months post-treatment, 12 months post-treatment, 18 months post-treatment, and 24 months post-treatment
- Product Enhancement recommendations: Day 56 for the EaseVRx-8w and EaseVRx-8w plus extended on-demand groups, and at 8-weeks post-treatment for the EaseVRx-8w plus extended on-demand group
- Treatment Compliance: End of treatment for the EaseVRx and Sham VR groups and 8-weeks post treatment for the EaseVRx plus on demand Library and Sham VR plus on demand Library groups.

9.2 Scientific Rationale for Study Design

The use of the two active control groups (Sham VR-8w, Sham VR-8w extended on-demand arms) in this randomized control trial will minimize biases related to the novelty of the hardware and immersion.

9.3 Justification for Dose

Based on previous research by AppliedVR and other researchers in the virtual reality therapeutic space, individuals have experienced success in pain management by using VR at least once daily, for 10-15 minutes, and as needed for breakthrough flares of pain. For those with significant career and family-related responsibility, AppliedVR recommends using the device once daily at night before bed.

9.4 End of Study Definition

The study will be considered complete at the time that the last participant performs the last survey. Participants are expected to remain in the study for 24 months after undergoing their respective treatment period (8 or 16 weeks). Participants who complete their 24-month follow-up survey (see Schedule of Activities, Section 5.2.) will be considered to have completed study participation.

10 SELECTION OF STUDY POPULATION

10.1 Inclusion Criteria

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

1. Male and female participants aged 18-85.
2. Self-reported diagnosis of chronic lower back pain.
3. Pain duration of at least three months.

4. Average pain intensity score of ≥ 4 and average pain interference score of ≥ 4 on the 0-10 BPI Pain Scale for the past month at screening.
5. Fluency in English.
6. Willing and able to comply with all study procedures including all required restrictions for the duration of study participation.
7. Able to give voluntary, written informed consent to participate and have signed an Informed Consent Form specific to this study.
8. Access to Wi-Fi for the duration of their study participation (24 months).
9. Access to a smartphone or computer for the duration of the study.
10. Availability of a physical mailing address that is not a PO box address for receipt of the device.
11. Completed the Baseline Survey plus at least two of the five sets of participant surveys that are administered during the 10-day pretreatment assessment period.
12. Able to provide photo ID.

10.2 Exclusion Criteria

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

1. Unable to understand the goals of the study due to cognitive difficulty.
2. Any medical condition that may prevent the use of virtual reality (e.g., current, or prior diagnosis of epilepsy, seizure disorder, hypersensitivity to flashing light or motion, migraines, any medical condition predisposing participant to nausea or dizziness, dementia, absence of stereoscopic vision or severe hearing impairment).
3. Injury to eyes, face, or neck that prevents comfortable use of VR.
4. Index back pain is linked to a cancer-related diagnosis.
5. Possible suicidal ideation as indicated by the 9th item of the participant Health Questionnaire-9 (PHQ-9).
6. Previous participation in the 2020 AVR EaseVRx pivotal study.
7. Receiving worker's compensation and/or involved in any active litigation related to an injury.
8. Current or recent participation (i.e., within the last 2 months) in any other research study involving a drug, device, vaccine, or other interventional treatment product; or plans to participate in another research study over the next 24 months.

10.3 Participant Recruitment and Screening

Participants will be recruited for this decentralized virtual trial via two methods.

Method 1: participants diagnosed with chronic lower back pain will be recruited from physician referrals through the Sponsor's relationships with physicians who treat chronic lower back pain in adult populations within the United States. Physicians seeing participants who appear to be a good fit for the study will refer the participants to the study by providing them with a pamphlet that provides a link to the study website, where they will have an opportunity to learn more about the study. Participants will

then be directed to Curebase where they will be asked to create a user account. After the creation of such an account, participants will be able to take a brief Eligibility Survey. If eligible to participate, participants will be asked to go through the consenting process. During the next 10 days, participants will be required to complete their baseline survey and at least 2 out of 5 brief surveys to become eligible for randomization.

Method 2: AppliedVR will also use direct email marketing and social media advertising to make potential participants aware of the study. The email and social media advertisements will provide a link to the study website, where they will have an opportunity to learn more about the study. Potential participants will be redirected to Curebase to sign an e-consent form and take the Eligibility Survey.

The total number of participants that were pre-screened (prior to consent), screened (post consent), and screen failed, including the reasons for screen failure, will be captured automatically in Curebase. Research staff will be able to report on this as needed.

10.4 Informed Consent

After passing the screener survey, prospective participants will be directed to review and sign an electronic HIPAA, California Bill of Rights (if a participant is located in California, and an IRB-approved consent (eConsent) form prior to enrolling in the study. The eConsent form will explain the nature and scope of the study, the procedures to be performed as part of the study, the potential risks, and benefits of participation, expected duration of participation, possible treatment alternatives, and an overview of his/her rights as a study participant in lay terms. Participants will have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. Participants will be informed that participation is voluntary and will be assured that they may withdraw from the study at any time and for any reason, without repercussion. The HIPAA, California Bill of Rights, and eConsent process will be via the study dashboard (hosted by Curebase, Inc.).

After viewing the eConsent materials, participants will have an opportunity to email or call the research team with any questions they may have and will be given as much time as needed to receive answers before making a final decision regarding study participation. Participants will receive a telephone number, email, and will have access to contact support staff as needed.

When the individual is ready to confirm their willingness to participate, an electronic signature will be collected to complete the eConsent formalities. The participant will receive a copy of the fully signed HIPAA, California Bill of Rights, and eConsent forms via email to retain for their records, and a digital copy will be retained within the Curebase system as part of the study records.

10.5 Screen Failures

A screen failure is a participant who consents but does not receive any of the study interventions due to withdrawing consent, being withdrawn from the study, or not meeting eligibility requirements for treatment.

If a participant signs the eConsent form but is found ineligible for inclusion in the study prior to or during the initiation of the study intervention, the participant will not be advanced any further in this clinical investigation and will be listed as a screen failure. The participant will be notified and the participant's signed eConsent form and updated inclusion/exclusion criteria details will be retained by the research team.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

To collect data related to CONSORT requirements, a Screening and Enrollment Log will be maintained. A research team member will review automated data from the eligibility survey on the Curebase dashboard.

11 STUDY PROCEDURES

11.1 Baseline Survey

After signing the eConsent form, participants will automatically be directed to complete a set of Baseline survey assessments that will include the following:

- Brief Pain Inventory - intensity/interference
- Oswestry Disability Index
- PROMIS Sleep Disturbance
- PROMIS Depression
- PROMIS Anxiety
- Concerns About Pain (CAP-6) Scale
- Behavioral Skills Use

Reminders will be sent approximately 1 hour and 24 hours after starting a survey to encourage the completion of Baseline surveys.

Twenty-four hours after completing the Baseline survey assessments, participants will be contacted with information about completing an optional incentivized set of surveys that include the following:

- Pain Self-Efficacy Questionnaire (PSEQ-10)
- Multidimensional Assessment of Interoceptive Awareness (Version 2)
- Multidimensional Health Locus of Control

Reminders will be sent approximately 1 hour and 24 hours after starting a survey to encourage optional survey completion.

Participants who filled out the Baseline Survey assessments will be contacted via an automated Curebase email/text to fill out at least 2 out of 5 pre-treatment BPI surveys over the next 9 days. *Note: Completion of these surveys is a pre-requisite for randomization*.

11.2 Enrollment & Randomization

Curebase will automatically direct the participant to a survey to provide a shipping address before participants complete the Baseline Survey assessments and two out of five sets of BPI surveys. Once the second BPI survey is filled out, the participant will be randomized into an arm of the study in 1:1:1:1 via Curebase and assigned a Participant ID number. The AppliedVR research team will arrange a device shipment based on the randomization assignment, and Curebase will notify the participant of the shipment tracking details.

11.3 Pre-Treatment Device Use Onboarding

Participants in the EaseVRx and Sham VR conditions will receive a PICO G2 4K headset with either EaseVRx or Sham content along with detailed instructions that will help them familiarize themselves with the hardware and software components. Telephonic and email technical support from study staff will be available to advise participants having trouble using the equipment. The participant will receive a reminder email to confirm VR headset receipt within 48 hours after FedEx tracking number was sent.

11.4 Treatment Phase (Weeks 0-8) & Extended Use Period (weeks 9-16)

Weeks 1-8: All participants will be instructed to use VR once a day for these 8 weeks. Research staff will monitor participants' progress through twice weekly BPI surveys and provide guided technical support. Device use can be monitored on a weekly basis for those participants who connect the device to Wi-Fi.

Weeks 9-16: For the 2 groups that are assigned to the arms with an extended 56-day on-demand period, participants will have the option of accessing VR for an additional 8-week period at their discretion. These groups will be instructed to use VR on an as-needed basis (i.e., there will be no set requirement for daily use as with the initial 8-week treatment phase).

11.5 Day 56

On Day 56, participants will complete their treatment phase and will be prompted to log onto the Curebase portal and complete the following assessments:

- Brief Pain Inventory - intensity/interference
- Oswestry Disability Index
- PROMIS Sleep Disturbance
- PROMIS Depression
- PROMIS Anxiety
- Participant Satisfaction
- Participant's Global Impression of Change Scale (PGIC)

- Concerns About Pain (CAP-6) Scale
- System Usability Scale (SUS)
- Behavioral Skills Use
- EaseVRx User Experience Questionnaire (and at week 16 in two arms with on demand Library)

Data Completion Reminders: Participants will be sent a reminder if they have not submitted data approximately 1 hour after starting a survey. Participants will also receive a reminder email or text message if they do not submit data approximately 24 hours after starting a survey. Research staff will make up to 3 call attempts to contact the participant to help get these surveys completed.

Twenty-four hours after completing the surveys listed above, participants will be contacted with information about completing an optional incentivized set of surveys that include the following:

- Pain Self-Efficacy Questionnaire (PSEQ-10)
- Multidimensional Assessment of Interoceptive Awareness (Version 2)
- Multidimensional Health Locus of Control

Reminders will be sent approximately 1 hour and 24 hours after starting a survey to encourage optional survey completion.

11.6 Post-treatment Data Collection

After Day 56, participants will be prompted to log onto the Curebase portal and complete the following assessments at 4-weeks, 8-weeks, 12-weeks, 6-months, 12-months, 18-months, and 24-months post-treatment:

- Brief Pain Inventory - intensity/interference
- Oswestry Disability Index
- PROMIS Sleep Disturbance
- PROMIS Depression
- PROMIS Anxiety
- participant's Global Impression of Change Scale (PGIC)
- Concerns About Pain (CAP-6) Scale
- Behavioral Skills Use

Data Completion Reminders: Participants will be sent a reminder if they have not submitted data approximately 1 hour after starting a survey. Participants will also receive a reminder email or text message if they do not submit data approximately 24 hours after starting a survey. Research staff will make up to 3 call attempts to contact the participant to help get these surveys completed.

Twenty-four hours after completing the surveys listed above, participants will be contacted with information about completing an optional incentivized set of surveys that include the following:

- Pain Self-Efficacy Questionnaire (PSEQ-10)
- Multidimensional Assessment of Interoceptive Awareness (Version 2)
- Multidimensional Health Locus of Control

Reminders will be sent approximately 1 hour and 24 hours after starting a survey to encourage optional survey completion.

11.7 Healthcare Utilization Analysis

To assess resource use associated with CLBP, participants' data will be run through a secure Datavant matching process to be linked to their healthcare claims data if it is available in the Komodo data set. The claims will provide descriptive characterizations of resource use and costs associated with CLBP. For participant-level changes in resource use, and for comparisons between study arms, only the participants with complete claims files will be assessed. Claims-matched data will capture all interactions with the healthcare system that generate an insurance claim record, which includes such things as physician visits, interventions such as steroid injections, surgery or physical therapy, emergent use of services, medications, and diagnostic procedures. Claims adjudication often lags a few months, so the most robust analyses of utilization will be performed about 6 months after the time point of interest (check with Komodo on adjudication/timing implications). Health economic modeling will be performed after 1 year to assess the cost and economic outcomes of the EaseVRx intervention.

The Komodo claims data provides a real-world source of utilization and cost parameters associated with claims of CLBP. As such, it can be used more broadly to either compare the study participants' resource use and costs to the broader population of participants with CLBP, or a "synthetic arm" can be constructed using available demographic data to match any of the study arms.

Additional details are detailed in a standalone Healthcare Utilization Analysis Plan.

12 STUDY INTERVENTION

12.1 Measures to Minimize Bias: Randomization and Blinding

The primary endpoint of this study will be collected via Electronic Data Capture and securely transmitted to the Database. Curebase will maintain the database and be responsible for all aspects of data management.

Participants, study statisticians and investigators will be blinded to treatment group assignment until after the last subject contributes their primary outcome at week 8 . Prior to the primary analysis, the database will be officially locked and signed off by the Sponsor and key stakeholders. Study participants will remain blinded to treatment group assignment until study completion.

12.2 Study Intervention Compliance

Compliance to the treatment protocol will be monitored using remote data uploads of survey logs if a headset is connected to Wi-Fi by the participant. For participants who do not connect their headset to Wi-Fi, compliance will be assessed post-intervention when the headset has been returned.

13 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

13.1 Discontinuation of Study Intervention

A small proportion of participants may find the headset uncomfortable, the VR experiences ineffective, or find themselves not using the device and wish to withdraw. Participants who report moderate to severe adverse events that prevent them from using the program will be discontinued. Discontinuation from the use of the VR program or Sham VR will not automatically trigger discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be recorded as an adverse event (AE).

13.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time and for any reason. A member of the research team will ask the participant for the reason for their withdrawal and will record all information regarding the participant discontinuation in their study records.

An investigator may also discontinue or withdraw a participant from the study for the following reasons:

- If any serious to severe adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
    - Participants who experience an SAE due to an undisclosed condition that would have prevented trial eligibility will be discontinued from the study and will be documented as an eligibility deviation.
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Any other problem deemed by the Investigator to be sufficient to cause discontinuation.

The reason for participant discontinuation from the study will be recorded.

13.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to complete two or more consecutive surveys and is unable to be contacted by the study site staff. Before a participant is deemed lost to

follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). If participants are not reached in these attempts, they will receive a final email asking them to complete a discontinuation form. These contact attempts and any discontinuation will be documented. Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

13.4 Equipment Return

Participants will not be financially responsible for damage to, or loss of, equipment loaned to participants by the research team during this study. However, if they are not able to return the headset at the end of the VR treatment, regardless of its condition, then they will not be eligible to receive their honorarium payment. Reminders will be sent via email and text at the end of VR treatment period (8-weeks or 16-weeks), and a call will be made if the device still is not returned after multiple reminders during a 14-day period. If the device is not returned, then the study team will document the reason for the participant not returning the device from the phone call (e.g., lost).

14 STUDY ASSESSMENTS

14.1 Efficacy Assessments

Primary Outcome

The primary outcome for this study will be the BPI questionnaire. The BPI questionnaire is a validated instrument with good content validity, construct validity, and reliability in participants with chronic pain. The range of scores are from 0-10. The BPI contains a single item related to pain intensity and 7 items related to pain interference. The BPI pain interference score is the mean of seven questions that assess pain interference on general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The higher the score the greater the impact of chronic pain on the participant.

Secondary Outcomes

Secondary outcomes include the Oswestry Disability Index score (ODI v2.1b), PROMIS Sleep Disturbance, PROMIS Depression, PROMIS Anxiety, and participant Satisfaction that will be evaluated before the intervention, immediately following the intervention (Day 56 in all arms), 4-weeks post-treatment, 8-weeks post-treatment, 12-weeks post-treatment, 6 months post-treatment, 12 months post-treatment, 18 months post-treatment, and 24 months post-treatment. participant Satisfaction will be evaluated on Day 56.

- **Oswestry Disability Index**
    - The Oswestry Disability Index (also known as the Oswestry Low Back Pain Disability Questionnaire) is a tool that researchers and disability evaluators use to measure a participant's functional disability. The test is considered the ‘gold standard’ of low back

functional outcome tools. The *tool is well validated with excellent content validity, construct validity and reliability.*

- **PROMIS Scales Sleep Disturbance, Depression & Anxiety**
    - For participants with chronic pain, sleep quality is often diminished, and participants seek return to normal function. The PROMIS® short-form scales are widely- validated instruments with excellent content validity, construct validity, and reliability in participants with spinal disorders and other conditions marked by diminished mobility. The sleep disturbance scale assesses perceptions of sleep quality, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. The depression scale assesses the pure domain of depression in individuals aged 18 and older. The anxiety scale assesses the pure domain of anxiety in individuals aged 18 and older. All PROMIS® measures use a 7-day recall period reflecting the previous week's health status.
- **Virtual Reality Sickness Questionnaire**
    - The Virtual Reality Sickness Questionnaire was developed for use as a motion sickness measurement index specialized for virtual reality environments. The 12 items measure such symptoms as dizziness and nausea with four response options (None to Severe).
- **Participant Satisfaction** (adverse effects and recommendations)
    - A custom survey was created to assess satisfaction with our VR program. Topics include device usability, enjoyment or difficulties, and likelihood to continue treatment.

Tertiary / Exploratory Outcomes

- **Participant's Global Impression of Change Scale (PGIC)**
    - This single item questionnaire is validated for use in studies to compare participant satisfaction between different treatment assignments.
- **Concerns About Pain (CAP-6) Scale**
    - This six-item scale represents the first item response theory-based item bank of pain catastrophizing. The measure is intended for clinicians interested in improving outcomes of participants with chronic pain and for researchers who study impact of and treatment interventions aimed at reducing pain catastrophizing.
- **Systems Usability Scale (SUS)**
    - The System Usability Scale (SUS) provides a reliable tool for measuring the usability of our VR program. It consists of a 10-item questionnaire with five response options (Strongly disagree to Strongly agree).
- **Behavioral Skills Use**
    - One major goal of the skills-based VR intervention (EaseVRx) is to facilitate the development of behavioral coping strategies in chronic pain sufferers that can be utilized outside of the VR headset. The research team has constructed a survey to assess the development of these skills. Specifically, participants will be asked whether they can

manage their pain outside of the VR headset using deep breathing, releasing unhelpful thoughts, redirecting attention, and self-compassion coping behaviors.

- **EaseVRx User Experience Questionnaire**
    - This is a questionnaire constructed to better understand the user experience, usefulness, and participant satisfaction with the VR therapeutic program and some of its features. It is a 19-multiple-choice-item questionnaire with 6 optional open-ended questions. This questionnaire will only be presented to participants in the skills based EaseVRx conditions.
- **Pain Self-Efficacy Questionnaire (PSEQ-10)**
    - The Pain Self-Efficacy Questionnaire (PSEQ-10) is a validated instrument used to assess participants' confidence in their ability to carry out their daily activities. The 10-item questionnaire asks participants to rate their confidence from 0 to 6 corresponding to not at all confident to completely confident.
- **Multidimensional Assessment of Interoceptive Awareness (Version 2)**
    - The Multidimensional Assessment of Interoceptive Awareness (MAIA-II) will be used to evaluate how interoceptive awareness relates to the other study's outcome measures by assessing participants' bodily sensation awareness. It consists of a 37-item questionnaire with 6 response options (never to always) for 8 state traits (e.g., noticing, body listening).
- **Multidimensional Health Locus of Control (MHLC-C)**
    - The Multidimensional Health Locus of Control (MHLC-C) will be used to help characterize participants, their health-related behaviors, and response to treatment. It is an 18-item scale evaluating health locus of control with four subscales: internal, doctors, chance, and other people.
- **Discontinuation of Treatment Questionnaire**
    - The Discontinuation of Treatment Questionnaire will only be used if a moderate adverse event occurs. This will give the participants the option to discontinue from the study and may pinpoint cause of discomfort, if any.

14.2 Other Assessments

- **Treatment Compliance**:
    - Data related to the frequency and length of time using the intervention will be stored on the virtual reality headset for the entire 8-week or 16-week period (depending upon the participant's arm in the study. The data will be sent back to the research team via connection to the participant's phone using mobile data, or when the headset is returned.
- **Perceived Treatment assignment Question**:
    - At the end of treatment for all groups, the research team will evaluate how expectations relate to our program's outcomes by assessing participants' beliefs about their group

assignments. The research team will also ask participants to report which VR program condition they believed they participated in.

- **Benefits Screening**:
    - At 12 months participants will be asked if they are currently receiving or have previously received/petitioned for disability or worker's compensation benefits. This will allow the research team to account for possible motivating factors for participants to report increased pain or have increased healthcare utilization during the course of the study.

14.3 Healthcare Utilization Assessments

Pain-related healthcare utilization will be assessed in a subset of participants for whom access to complete insurance claims files are available. All claims for medical care associated with CLBP will be included and includes claims for the following types of services:

- Number and type of imaging and diagnostic procedures
- Number and type of health care practitioner visits including specialty care
- Number of chiropractic and physical therapy visits
- Number and type of emergency room visits
- Number and type of surgeries,
- Number, type, and duration of hospitalizations
- Frequency of 30-, 60-, 90- day readmissions
- Complications that can be assigned to the pain or pain-related interventions

Clinical outcomes and health care utilization data captured will include billed and paid claim amounts and can be used to in modeling to demonstrate the economic value of the product.

15 PROTOCOL DEVIATIONS

Conformance to the protocol is essential to the quality and integrity of the clinical study. A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the research team.

It is the responsibility of the study investigators to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within ten working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing IRB per their policies. The study investigators are responsible for knowing and adhering to the reviewing IRB requirements.

16 SAFETY REPORTING

Participants will be carefully monitored during the study for possible adverse events (AEs) from the time they start treatment or sham to the time of study completion. All medical events and conditions prior to

this time point are to be captured as medical history. Any observed AE will be fully investigated by the Investigator and classified in line with the definitions below.

All adverse events that occur during this study will be recorded on the adverse event eCRFs and must include the following information at minimum:

- Event Description
- Date of Onset
- Date of Resolution
- Severity
- Seriousness
- Relationship to Study Device/Procedure
- Outcome

Adverse events will be recorded and classified by the research team, including a medical doctor on staff, using the specific signs, symptoms, or medical diagnosis if no signs or symptoms can be identified.

Significant new information and updates should continue to be captured in the participant's records and in the EDC as they become available and the adverse event should be followed until it is resolved or no further improvement is expected, or the participant is lost to follow-up. The Investigator will record all AEs regardless of whether they are anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome, or causality.

16.1 Definitions

Adverse Event (AE): any untoward medical occurrence, disease, injury, or untoward clinical signs (including abnormal laboratory findings, surgical complications, etc.), whether related or unrelated to the investigational device or its use.

Adverse Device Effect (ADE): An adverse device effect (ADE) is any adverse event related to the use of an investigational device.

Serious Adverse Event (SAE): A Serious Adverse Event is an adverse event which:

1. Led to a death
2. Resulted in life threatening illness or injury
   NOTE: the term 'life-threatening' refers to an event in which the participant was at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
3. Resulted in in-participant hospitalization or prolonged hospitalization
   NOTE: Planned hospitalization for any pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.
4. Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5. Resulted in participant disability or permanent damage or required intervention to prevent permanent impairment/damage
6. Led to a congenital abnormality or birth defect

Unanticipated Adverse Device Effect (UADE) – An Unanticipated Adverse Device Effect is:

- Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this protocol; or
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the participants.

16.2 Assessment of Severity

The Investigator will assess the severity of the adverse event and classify it according to the following definitions:

Severity	Description
Mild	Symptoms are tolerable, involve no more than mild discomfort and subside shortly after removing the headset; no medical attention is required. Participants report a desire to continue using the headset.
Moderate	Symptoms last for a subjective significant period after removing the headset and may require minimal medical attention (e.g., to reduce severe headache). Participants may or may not report a desire to discontinue the study intervention.
Severe	Symptoms have enough of an impact to prevent further use of the headset or involve a limitation in ability to function (e.g., participant can't walk); medical attention is required/hospitalization possible. Participants report a desire to discontinue the study intervention.

These definitions are for descriptive purposes only and are independent of the judgment of whether an event is classified as serious or non-serious.

16.3 Assessment of Relationship

The relationship between the use of the medical device and the occurrence of each adverse event shall be assessed and categorized. During causality assessment, clinical judgment shall be used, and the Clinical Protocol shall be consulted, as all the foreseeable adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The term "device-related," as it pertains to adverse events, means that the event was or may have been attributable to a device, or that a device was or may have been a factor in an event, including those occurring as a result of malfunction, poor manufacture, inadequate labeling, or improper design.

The Investigator will assess the potential relationship of the AE to the use of the investigational device and classify the causality of the event according to the following definitions.

- Related: An adverse event that has a strong causal relationship. An adverse event that follows a strong temporal relationship to the use of the device, follows a known response pattern, and cannot reasonably be explained by known characteristics of the participant's clinical state or other therapies.
- Probably Related: An adverse event that potentially has a causal relationship. The adverse event has a reasonable temporal relationship to the use of the device and alternative etiology is less likely compared to the potential relationship to the use of the device or the procedure.
- Possibly Related: An adverse event that potentially has a causal relationship. The adverse event has a reasonable temporal relationship to the use of the device, but alternative etiology is equally likely compared to the potential relationship to the use of the device or the procedure.
- Not Related: An adverse event without any apparent causal relationship. The adverse event is due to the underlying disease state or is due to concomitant medication or therapy not related to the use of the device.
- Unknown Relationship: If the adverse event cannot be determined to have a causal relationship, it will be classified as unknown.

16.4 Adverse Event Reporting

The collection of AEs will begin as soon as the participant first puts on the VR headset for this study. All AEs that occur through completion of the final follow-up visit, whether or not thought to be device related, should be recorded in detail and followed to resolution.

The description of the AE will include the date and time of onset, severity, relationship to the use of the device, the results of any diagnostic procedures or laboratory tests, if any treatment was required, and the outcome of the event. The AVR research team will follow each participant who experiences an AE until the event resolves, resolves with sequelae, or no further improvement is expected. In the unusual circumstance that an AE has not resolved by the time the participant completes the study, an explanation will be entered in the study database.

Note: Any condition at baseline that is recorded as a preexisting condition is not an AE unless it worsens in intensity or duration.

16.5 Serious Adverse Event Reporting

The Sponsor is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in line with US regulatory requirements.

It is the responsibility of the Investigator to report all SAEs and UADEs according to FDA regulations and IRB requirements. A copy of the IRB report should be forwarded to the TMF.

16.6 Determination and Reporting of Unanticipated Adverse Device Effects

The Sponsor shall review all reported SAEs to evaluate whether they meet the criteria for an Unanticipated Adverse Device Effect (UADE). For adverse events that are determined to be UADEs, the Sponsor will submit an expedited safety report to the FDA's Center for Devices and Radiological Health (CDRH). The expedited safety report will be submitted to the FDA as soon as possible and, in no event, later than ten (10) business days after the Sponsor first receives notice of the UADE. A copy of this safety report will be provided to the reviewing IRB and all participating study Investigators.

If, following receipt and investigation of follow-up information regarding an adverse event that was previously determined not to be a UADE, the Sponsor determines that the event does meet the requirements for expedited reporting, the Sponsor will submit a report as soon as possible, but in no event later than ten (10) business days after this is determined.

To determine whether an UADE presents an unreasonable risk to study participants, the Sponsor will:

- Immediately investigate and evaluate the adverse effect (21 CFR § 812.46(b)(1));
- If the event presents, an unreasonable risk to participants, shall terminate the investigation, or parts of the investigation presenting that risk as soon as possible, and no later than 5 business days after the Sponsor makes the "unreasonable risk" determination, and no later than 15 business days after the Sponsor receives notice of the UADE;
- Resume the study, if appropriate, when permitted by the IRB and FDA;
- Notify FDA of event and any action taken by the Sponsor as a result of this UADE.

16.7 Device Deficiency Reporting Procedures

Device deficiencies will be documented and reported to AppliedVR by the technical support staff if a complaint is received from a participant. If possible, the device(s) should be returned to the Sponsor for analysis. Instructions for returning the device(s) will be provided to the participants by the technical support team.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate CRF.

Investigators will be expected to report the following information for each device deficiency:

- Date deficiency discovered
- Type of deficiency (e.g., malfunction, use error, inadequate labeling)
- Description of the deficiency

17 STATISTICAL CONSIDERATIONS

All statistical considerations are detailed in a standalone Statistical Analysis Plan.

18 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

18.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study participants, investigators, and sponsors. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor or IRB.

18.2 Confidentiality and Privacy

Participant privacy is strictly held in trust by the participating investigators, their staff, and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without the prior written approval of the Sponsor.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator for the participants in this study.

Data in the study is collected in two ways: in real-time and at infrequent intervals throughout the study. Real-time data, including survey data delivered via mobile device or computer, will be stored on secure servers hosted by Curebase and will contain only a unique identifier for each participant. Virtual reality adherence data will also be tracked in real-time and hosted on secure servers by AppliedVR, and a separate unique ID will be assigned to each participant. Data collected at infrequent intervals throughout the study, such as entry, weekly, and exit questionnaires will be stored on secure servers with unique IDs for each participant. Each dataset will utilize different unique IDs and a list linking each unique ID to each participant will be stored internally on the secured network. The linking list allows a researcher with access to the secured files to merge all data using statistical software while maintaining data confidentiality.

Healthcare utilization data for a subset of the study participants will be accessed in collaboration with Komodo Health. We will use the Datavant service, which generates a one-way cryptographic hash to ensure that tokenization cannot be reversed, in a process certified by leading HIPAA experts. Security controls ensure that no one (including the Datavant and Komodo teams) can get access to participants' protected health information (PHI) or study data without permission. Tokens act as keys that can be used to link the same individual's data without sharing identifying information.

18.3 Publication and Data Sharing Policy

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

This trial will be registered at ClinicalTrials.gov in compliance with 42 CFR Part 11, and results information from this trial will be submitted to the ClinicalTrials.gov database at the conclusion of the study. In the event that the study is terminated early, the posting of these results will be completed within 30 days of completion of data analysis. In addition, every attempt will be made to publish results in peer-reviewed journals.

18.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership, in conjunction with the IRB, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

18.5 Study Records Retention

The Sponsor will maintain accurate, complete, and current records relating to this clinical investigation.

Upon study completion, the study files will be maintained in a known location for a maximum of a two-year period after the device's marketing approval is issued by FDA in accordance with US regulatory requirements.

The Sponsor will maintain records in accordance with 21 CFR 812, Subpart G, to include:

- Current and past versions of the IRB-approved clinical protocol and amendments
- IRB-approved consent materials and participant recruitment advertisements
- IRB correspondence (including submissions and approval notifications) including safety and protocol deviation reports, and annual or interim reports
- Signed Investigator Agreements and financial disclosure forms for participating Investigators
- Curriculum vitae for all Investigators

- Certificates of required training for Investigators, including human subject protection and Good Clinical Practice
- Instructions for handling the investigational device and other study-related materials
- Device tracking logs
- Signed consent records
- eCRF and Source Documents
- Screening and Enrollment Log
- Final clinical study report

19 REFERENCES

1. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001-1006. doi: 10.15585/mmwr.mm6736a2. PubMed PMID: 30212442; PMCID: PMC6146950.
2. "Opioid Drugs: Global Markets to 2023." Market Report. BCC Research, 2018
3. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain. 2015;16(8):769-780. doi: 10.1016/j.jpain.2015.05.002. PubMed PMID: 26028573; PMCID: PMC4562413.
4. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC)2011.
5. Interagency Pain Research Coordinating Committee. National pain strategy: a comprehensive population health-level strategy for pain. National Institutes of Health, US Department of Health and Human Services; 2016.
6. Reuben DB, Alvanzo AA, Ashikaga T, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. Ann Intern Med. 2015;162(4):295-300. doi: 10.7326/M14-2775. PubMed PMID: 25581341.
7. O'Brien EM, Staud RM, Hassinger AD, et al. participant-centered perspective on treatment outcomes in chronic pain. Pain Med. 2010;11(1):6-15. doi: 10.1111/j.1526-4637.2009.00685.x. PubMed PMID: 19732374.
8. Moore RA, Derry S, Simon LS, Emery P. Nonsteroidal anti-inflammatory drugs, gastroprotection, and benefit-risk. Pain Pract. 2014;14(4):378-395. doi: 10.1111/papr.12100. PubMed PMID: 23941628; PMCID: PMC4238833.
9. Spiegel B. Virtual Reality for Management of Pain in Hospitalized participants: A Randomized Comparative Effectiveness Trial (unpublished).
10. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use-United States, 2006-2015. MMWR Morbidity and mortality weekly report. 2017;66(10):265-269. doi: 10.15585/mmwr.mm6610a1. PubMed PMID: 28301454 PMCID: PMC5657867
11. Garcia, LM, Birckhead, BJ, Krishnamurthy, P, Sackman, J, Mackey, IG, Louis, RG, Salmasi, V., Maddox, T, & Darnal, BD. An 8-week self-administered at-home behavioral skills-based virtual reality program for chronic low back pain: Double-blind, randomized, placebo-controlled trial conducted during COVID-19. JMIR, 2021;13(2):e26292 *doi:10.2196/26292*
12. Darnall, B. D., Krishnamurthy, P., Tsuei, J., & Minor, J. D. (2020). Self-Administered Skills-Based virtual reality intervention for chronic pain: randomized controlled pilot study. *JMIR formative research*, *4*(7), e17293.