Safety and Effectiveness of Virtual Reality utilizing EaseVRx for the Reduction of Chronic Pain and Opioid Use

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TABLE OF CONTENTS

1 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
AE	Adverse event
BMI	Body Mass Index
CBT	Cognitive behavioral therapy
CDC	Centers for Disease Control
CPAQ-8	Chronic Pain Acceptance Questionnaire
EHR	Electronic Health Record
GHP	Geisinger Health Plan
GIRB	Geisinger IRB
IPRPs	Interdisciplinary Pain Rehabilitation Programs
IRB	Institutional Review Board
MME	Milligrams of morphine equivalent
MRN	Medical Record Number
NPRS	Numerical Pain Rating Scale
ODI	Oswestry Disability Index
OUD	Opioid Use Disorder
PCS-4	Pain Catastrophizing Scale
PSEQ-10	Pain Self-Efficacy Questionnaire
PDMP	Pennsylvania Prescription Drug Monitoring Program
PROMIS	Patient Reported Outcomes Measurement Information System
SAE	Serious adverse event
SF-12	12-item Short Form Health Survey
SoC	Standard of Care
VR	Virtual Reality

2 ABSTRACT

EaseVRx™, a software-based virtual reality (VR) medical device, is intended to offer users a prescription pain management tool that manages the symptoms associated with chronic pain and reduces or eliminates the risk of opioid dependence. EaseVRx is based on principles of cognitive behavioral therapy, pain psychology, mindfulness-based stress reduction, biofeedback, and distraction therapy commonly used in interdisciplinary pain rehabilitation programs. We will conduct a proof-of-concept randomized, double-blind, placebo-controlled study to assess the feasibility and efficacy of using EaseVRx as an 8-week, VR-based, at-home program among 100 chronic low back pain patients by gathering pilot data on the efficacy of the intervention in decreasing pain, reducing opioid/non-opioid pharmacotherapy, and improving pain-related quality of life. While VR has been tested in academic medical centers and shown to be efficacious in the management of acute pain, this study will investigate the feasibility of VR use at home to manage chronic pain in preparation for a larger efficacy trial.

3 BACKGROUND AND SIGNIFICANCE

3.1 Chronic pain: an epidemic representing a major unmet medical need.

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 is traditionally based primarily around utilizing pharmacological management tools, which typically involves opioids. Although some non-opioid pharmaceuticals and non-pharmacological therapies are becoming available, there is still significant unmet need for integrative, 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 patients 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 patient 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 patient developing a dependency within a year[10].

Opioids have a significant adverse event profile that includes hypotension, respiratory depression or arrest, aspiration, and/or vomiting. Although these risks are manageable, it is imperative to devise pain alternatives that are cost-effective and improve the risk-benefit profile well above the current standard of care. To reduce addiction and provide relief for the millions of chronic pain sufferers, new low-risk, non-opioid pain analgesics are needed.

3.2 appliedVR's answer for chronic pain: EaseVRx

Therapeutic VR has emerged as an effective, non-pharmacological treatment modality for pain[9]. VR users wear a pair of goggles with a close-proximity screen that creates a sensation of being transported into immersive, three-dimensional worlds. One hypothesis for VR's mechanism of action proposes that by stimulating the visual cortex while simultaneously engaging other senses, VR is able to limit the user's processing of pain signals[9].

The common nature of mobile high-performance computing has now reduced both the size and cost of VR devices, allowing for VR use in everyday settings like the clinic and at home. As an alternative to opioids, VR has been proven to be effective in decreasing pain during severe burn wound bandage changes, IV line placements, and dental interventions[9].

Unlike opioids, VR has a reduced risk of the user developing a dependency or addiction to the pain management technique. If a patient can utilize VR for pain management, they can either reduce or potentially remove the need for opioid or other pharmacological management

techniques. This sparing of opioid use greatly reduces the risk of the patient developing OUD or addiction.

appliedVR's investigational EaseVRx product for chronic pain is based on principles of cognitive behavioral therapy (CBT), pain psychology, mindfulness-based stress reduction, biofeedback, and distraction therapy commonly used in interdisciplinary pain rehabilitation programs (IPRPs). These programs often include physical and occupational therapy; exercise therapy; cognitive restructuring with an emphasis on promotion of self-management, self-efficacy, resourcefulness, and activity versus passivity, reactivity, dependency, and hopelessness; behavioral treatment (e.g. relaxation, activity pacing); and opioid tapering and management. The reduction of pain after treatment at IPRPs has been reported to be significant in several metanalyses[12-14], with one meta-analysis[12] reporting that the mean pain reduction for patients treated at IPRPs was 37% with a concomitant significant decrease (63%) in prescription pain treatment. Moreover, one early metanalysis of 42 published studies[15] reported significant reductions in health-care use after treatment at IPRPs.

Access to interdisciplinary chronic pain management programs is seriously lacking in the United States. In 1999, it was estimated that there were over 1000 interdisciplinary pain management programs in the United States[16]. This number has dropped dramatically to 150 in 2011[17]. Based on the number suffering from chronic pain, this data suggests there is approximately one interdisciplinary program for every 670,000 chronic pain victims in the United States. EaseVRx is a simple, low-risk, non-invasive device with the potential to become a ubiquitous pain management therapy to address the lack of access to interdisciplinary care. In view of the complex nature of chronic pain, treatment often necessitates use of a blend of different approaches with a focus on maximizing symptom relief so that patients are able to lead the highest quality of life possible.

This study will evaluate the degree and duration of analgesic effect on chronic low back pain from use of the EaseVRx device. To control for any potential placebo therapeutic effect that may be experienced merely by donning a VR headset, a sham VR control group is included in the study design. The VR sham product will consist of a void theater, which is defined as a 2D virtual screen in front of the user that displays a variety of video content. The screen will be surrounded by a solid black environment to minimize immersion. The user experience is best described as being inside of a pitch black movie theater. The content displayed in the void theater will be a variety of 2D nature-related content that is not intended to have therapeutic effect. The VR sham user interface and functionality will be designed to mirror the user interface and functionality of the EaseVRx intervention.

4 HYPOTHESIS AND SPECIFIC AIMS

4.1 Primary Aim 1

Compare pain and pain coping skills among the VR sham and the EaseVRx group. *Hypothesis: Chronic low back pain patients randomized to the EaseVRx approach who use the device in accordance with the treatment protocol will have significantly decreased pain scores and improved pain coping skills 4, 8, and 12 weeks after starting the 8-week VR treatment.*

4.2 Secondary Aim 1

Compare physical function as measured by the Oswestry Disability Index (ODI) among the VR sham and EaseVRx group. *Hypothesis: Chronic pain patients randomized to the EaseVRx approach who use the device in accordance with the treatment protocol will have significantly better physical function (i.e. lower ODI scores) 4, 8, and 12 weeks after starting the 8-week VR treatment.*

4.3 Secondary Aim 2

Compare analgesic medication use among the VR sham and EaseVRx group. *Hypothesis: Chronic pain patients randomized to the EaseVRx approach who use the device in accordance with the treatment protocol will have decreased utilization of opioid and non-opioid pharmacotherapy 4, 8, and 12 weeks after starting the 8-week VR treatment.*

4.4 Secondary Aim 3

To assess the feasibility of EaseVRx as a self-administered, home-based approach to chronic pain management, in terms of patient compliance, program retention, patient satisfaction, and safety. *Hypothesis: EaseVRx will be a feasible approach to chronic pain management, with high rates of patient compliance, retention, and satisfaction among chronic pain patients after completing an 8-week course of treatment with EaseVRx.*

4.5 Secondary Aim 4

Compare healthcare cost and utilization among the VR sham and EaseVRx group among patients with Geisinger Health Plan as their primary insurance. *Hypothesis: Chronic pain patients randomized to the EaseVRx approach who use the device in accordance with the treatment protocol will have significantly lower costs and utilization (i.e. office visits, therapy sessions, inpatient/ED admissions) 3 months, 6 months, and 12 months after starting the 8-week VR treatment.*

5 PRELIMINARY DATA

appliedVR has conducted two small-scale feasibility pilots to understand the acceptability, usability, and satisfaction of EaseVRx on various chronic pain conditions. Both studies provided subjects with the use of an 8-session VR intervention at home. The first pilot measured the preliminary EaseVRx program among 45 chronic pain users of various diagnoses. Surveys were administered for 8 days prior to the intervention to establish a baseline measure of pain and quality of life using the PROMIS Global-10. Pain intensity and interference were also measured daily using the Numerical Rating Scale and Department of Defense/Veterans Administration Pain Supplemental Questions. Findings from this pilot showed participants generally experienced reduction in their pain levels over the 8-day-course of use, particularly in the interference of pain with their mood. On average, participants showed a 22% improvement in pain, 24% improvement in stress, 29% improvement in mood, and 25% improvement in sleep quality (over baseline).

A second, targeted quantitative and qualitative study was conducted to assess pain relief and durability, quality of life impact, and engagement of the 8-session VR program among 30 chronic pain patients with a musculoskeletal pain diagnosis (back, spine, neck or joint pain) or rheumatoid arthritis. Outcomes collected included pain intensity via the Numerical Rating Scale, PROMIS Pain Interference Short Form 6b, PROMIS Sleep Disturbance Short Form 4a, and Stanford Expectations of Treatment Survey. Subjects were also given a brief semi-structured interview after completion of the program to understand their satisfaction and challenges with the VR intervention. Subjects who completed six or more modules improved, on average, across every measured Quality of Life metric. On average, users showed 22% reduction in pain intensity over the course of the program.

6 STUDY DESIGN

6.1 Description

This is a single-center, prospective, randomized, double-blind, placebo-controlled study of the appliedVR EaseVRx headset in subjects with chronic lower back pain. A cohort of 126 patients will be recruited from patients currently seeking care for low back pain at Geisinger. We are assuming a 20% dropout or noncompletion rate, so recruiting 126 patients should provide 100 completes. Patients with moderate to severe chronic low back pain who have largely exhausted non-pharmacological approaches to improving pain and who are currently relying primarily on pharmacotherapy for symptom relief will be recruited for the study. These patients are an ideal study population to include as few treatment options remain for these patients due to insufficient understanding of pain origin, failure of conventional pain management approaches, or unsuitability of surgical interventions. Patients will be randomized by computer 1:1 to either the VR sham or EaseVRx group. Providers and patients will be blinded in regard to whether the patient will receive EaseVRx or the VR sham.

6.2 Study Population

6.2.1 Approximate Number of Subjects

Approximately 126 Geisinger subjects will participate in this study (63 in each study arm).

6.2.2 Inclusion Criteria

- Inclusion criteria include:
    - Able and willing to provide written informed consent
    - Ages 18 to 64 years (inclusive)
    - Based on medical history (including available medical records), chronic low back pain must have been present for at least 3 months
    - Completed at least 4 weeks of non-surgical pain management and physical therapy with no apparent benefit
    - Has a mean NPRS pain score that is ≥ to 4 (without rounding) over the 7-day screening period

- Subject has a score of 1-3 based on the American Society of Anesthesiologists Physical Status Classification System
- Agrees to comply with all study requirements throughout the entire study period

Exclusion Criteria

- *Exclusions based on potential medical or lifestyle confounders:*
  - Has a body mass index (BMI) > 40 kg/m2
  - Pain related to cancer, fibromyalgia, or disk herniation
  - History of a major psychiatric disorder not controlled with medication or has behavioral factors that would interfere with proper study procedures
  - Is not ambulatory/has significant motor impairment
  - Surgery in the past 3 months
  - Open workers compensation claim
  - Planning to have surgery in the next 3 months
  - Planning to start a new exercise program in the next 3 months
  - Planning to start a new treatment for their pain (e.g. medication, physiotherapy, acupuncture, electrical nerve stimulation) in the next 3 months
- *Exclusions based on potential drug-related cofounders:*
  - Current or recent history (in past year) of substance abuse disorder
  - Currently pregnant/breastfeeding or planning to in the next 3 months
  - Was administered an epidural steroid during the 3 months prior to screening
- *Exclusions based on ability to use EaseVR effectively:*
  - Comorbidities including neurological, psychosocial, sensory, or other disorders that may impact pain perception
  - Diagnosis of epilepsy, dementia, migraines, or other neurological disorders that may prevent VR usage, and/or other medical conditions predisposed to nausea and dizziness
  - Hypersensitivity to flashing lights or motion
  - Claustrophobia
  - Lack of stereoscopic vision
  - Severe hearing impairment
  - Injury to eyes, face, or neck that prevents comfortable VR usage
  - Planning to take a vacation from their home for more than one week in the next 8 weeks

6.3 Recruitment

The primary and collaborating investigator(s) will identify potential subjects in the Geisinger system who are scheduled for a clinic visit to address their chronic low back pain. These patients will be pre-screened via manual chart review of their electronic health record (EHR) by the research team. Patients meeting the inclusion/exclusion criteria will be called by an IRB-approved study team member (e.g. primary and collaborating physicians, research project coordinator, research assistant) approximately one week prior to their scheduled clinic visit. After hearing a description of the study and completing a short screening assessment, eligible

patients will be asked to report their average lower back pain over the last 24 hours via a Numeric Pain Rating Scale (NPRS) score for 7 days. Each subject will choose how they want to report their daily NPRS scores and will be giving the following options: phone calls, texts, or web-based entry via REDCap. They will be instructed to record their scores at the same time each day (± 2 hours).

At the end of the 7-day screening period, the study team will assess daily NPRS scores to determine if the subject meets the pain eligibility requirements: (1) subjects must complete at least 5 of 7 daily NPRS scores in the previous 7-day screening period and (2) the overall average NPRS score must remain between 4 and 10 (inclusive) during the screening period. Subjects who are deemed eligible will be approached by a member of the study team during their clinic visit to provide more information about the study and administer informed consent for interested patients.

6.4 Study Duration

6.4.1 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 12 months. This includes the baseline visit, the 8 weeks completing the VR modules, the 4-week follow-up period, and the final retrospective data pull at 12 months.

6.4.2 Approximate Duration of Study

This study will be completed in approximately two years. The end of the study is the last visit of the last subject or end of collection of data from the patient's electronic health record.

6.5 Procedures

After informed consent, patients will be randomized by computer 1:1 to either the VR sham or EaseVRx group. Providers and patients will be blinded in regard to whether the patient will receive EaseVRx or the VR sham device. The headset will be provided by a study team member during the clinic visit, along with device paper education materials. The patients will be instructed to not use the device while ambulating. The EaseVRx and VR sham devices will be presented in the context of an alternate method of pain control to opioids or other pharmacology. The patients will be assured they may receive the standard of care (SOC) for pain control in addition to the device. SOC pain management will follow pre-established clinical guidelines, and the additional VR-based or sham device will be made available but with no restriction on the use of other pain management methods as desired by the subject and prescribed by his/her provider.

All research activities will be conducted remotely after the initial baseline study visit. Each subject will be asked to complete an 8-week program with assigned modules each week. Each week, subjects will be asked to complete 5 modules, averaging 6 minutes in duration and ranging from 2 to 16 minutes in duration. At the end of the 8-week program period, participants will be asked to mail their device back to appliedVR using a provided, postage-paid mailer.

All outcomes will be assessed at the initial baseline visit and then every 4 weeks for 12 weeks via phone or online questionnaires. A core subset of these outcome measures, mainly pain and use of analgesic medications, will be collected daily during the 8-week program. Patients will be asked to complete a paper or online REDCap diary to track their pain levels, opioid/non-opioid pharmacotherapy, and device use from home. The daily log will capture the NPRS at the same time each evening (± 2 hours). Participants will be asked to record their NPRS at least 2 hours after taking any pain medication. Medication use will be recorded in terms of medication type, dose, and time of administration.

Outcomes data also may be collected via REDCap, a secure research electronic data capture system, or OBERD, a software system for patient-reported outcomes already in use at the study clinics. To assess opioid use, the investigators will query Pennsylvania's Prescription Drug Monitoring Program (PDMP) database. To maintain compliance with ABC-MAP Act 191 of 2014, study investigators will query the PDMP only for their existing patients. Patient clinical information will be extracted from their electronic medical records, including patient demographics, medical history and prescription information.

The EaseVRx devices will collect information related to device usage (i.e. frequency and duration of use, features utilized, completion rates). Patients may be contacted via phone or email by the study team to further encourage participation.

Outcome measures include:

- **Program Feasibility**:
    - Patient compliance will be assessed in two ways:
        - Treatment dose (actual minutes of VR or sham use per day); and
        - Treatment duration (actual number of days VR or sham used).
    - Program retention will be evaluated by the number of days that participants completed all outcome assessments.
    - Patient satisfaction will be assessed once at the end of the program by asking the participant four questions to evaluate the program:
        - Please tell me if you agree or disagree with the following statements: [strongly agree, somewhat agree, somewhat disagree, strongly disagree]
        - The VR headset was easy to use.
        - I enjoyed using the VR headset.
        - The content in the VR headset helped me cope with my chronic pain.
        - Today, on a scale of 1 to 10, where 1 means you would definitely NOT recommend VR treatment and 10 means you WOULD definitely recommend VR treatment, how likely are you to recommend VR treatment to someone else?
    - Patient safety will be assessed by monitoring subjects for the occurrence of adverse events (AE).

- **EaseVRx Efficacy**:

- Pain will be assessed via the standard Geisinger Numerical Pain Rating Scale (NPRS) ranging 0-10 (0 = least amount of pain, 10 = worst amount of pain).
- Pain Coping Skills will be assessed via:
  - Pain Self-Efficacy Questionnaire (PSEQ-2)[114, 115], which measures the confidence people with ongoing pain have in performing activities while in pain;
  - Pain Catastrophizing Scale (PCS-4)[116], which measures the impact of catastrophizing on the pain experience; and
  - Chronic Pain Acceptance Questionnaire (CPAQ-8)[117, 118], which measures the ability to accept and cope with chronic pain.
- Physical function will be assessed using by the Oswestry Disability Index (ODI).
- Analgesic medication use will be assessed in two ways:
  - Extrapolating total milligrams of morphine equivalent doses filled from PDMP database as an indicator of chronic opioid use; and
  - Patient self-reported consumption.
- Quality of life will be assessed using the 12-item Short Form Health Survey (SF-12).

- **Healthcare Cost and Utilization** *(Geisinger Health Plan patients only):*
  - Utilization will be assessed by recording the number of office visits, admissions, emergency room visits, and therapy sessions related to the patient's lower back pain for 12 months. Total milligrams of morphine equivalent doses filled from PDMP database also will be tracked.
  - Cost will be assessed by recording actual total amounts allowed by Geisinger Health Plan (GHP) and paid to the health system, by both insurer and patient, for utilization, medication, and other costs related to the patient's lower back pain.

6.5.1 Study Time and Events Table

Study Procedures	Day 0 (baseline visit)	Daily for 8 weeks*	4 weeks*	8 weeks*	12 weeks*	6 and 12 months**
Physical examination (office visit)	X					
Review inclusion/ exclusion	X					
Demographics, medical history	X					
Informed consent	X					
Randomization	X					
User instructions	X					
NPRS pain score	X	X	X	X	X	
PSEQ-2, PCS-4, CPAQ-8, ODI, SF-12	X		X	X	X	
Program satisfaction questions				X		
Analgesic drug use	X	X	X	X	X	X
Utilization and cost					X	X
Device utilization statistics[1]		X				
AE / Complication Reporting	X	X	X			

1 EaseVRx and sham VR groups only
** Data collected from patient at home via phone or online; not an in-person visit*
*** Retrospective review only*

6.6 Primary Endpoints

Primary endpoints include 1) the percent change from baseline (defined as the average of the 5- 7 pain scores obtained in the week prior to enrollment/randomization) in the average daily low back NPRS score during weeks 1-4 and weeks 1-8. The primary analysis will compare the EaseVR group against the VR sham group.

6.7 Secondary Endpoints

Secondary outcome measures include:

- Average daily minutes of VR or sham use at during weeks 1-4 and weeks 1-8.
- Number of days VR or sham used.
- Number of days that participants completed all outcome assessments.
- Patient satisfaction score (min 3 – max 12).
- Likelihood of recommending VR treatment to someone else (min 1 – 10 max).
- Number of adverse events related to the study treatment.
- Change from baseline PSEQ-2, PCS-4, CPAQ-8, SF-12 score at 4, 8, and 12 weeks.
- Change from baseline in total ODI score as well as subscale scores at 4, 8, and 12 weeks.
- Average self-reported daily amount of analgesic medication used during weeks 1-4 and weeks 1-8.
- Total milligrams of morphine equivalent doses filled from PDMP database at 3 months, 6 months, and 12 months.
- Total number of office visits, admissions, emergency room visits, and therapy sessions related to the patient's lower back pain at 3 months, 6 months, and 12 months.
- Total cost of care related to patient's lower back pain at 3 months, 6 months, and 12 months.

6.8 Statistics

A Geisinger statistician will complete the statistics. All statistical analyses will be performed with SAS (SAS 9.4, SAS Institute, Cary, NC), Stata (SE 14.2, StataCorp, LLC, College Station, TX), or R (R 3.5.2, The R Foundation, Vienna, Austria) statistical software, with p-values of <0.05 considered statistically significant.

6.8.1 Statistical Analysis Plan

We will calculate frequencies for categorical data and means with standard deviations for continuous variables. Bivariate comparisons will be explored using Chi-square or Fisher's exact test for categorical variables and two-sample t-tests or Mann-Whitney tests for continuous variables.

Because pain is expected to decrease over time, and because pain scores may vary by day and time of day administered, we will plan to plot NPRS score vs. time for every patient over the 8-week treatment period, using straight-line interpolation between measurements, which will allow us to use all available measurements (even if some patients recorded more NPRS scores than others) and will avoid placing too much emphasis on a measurement at a single time point (e.g. the 21-day measurement). We will compute a percent-area-under-the-curve (NPRS-%AUC)

measurement where 100% would indicate pain scores of 10 across the entire time period. Each patient will have a different NPRS-%AUC, forming a distribution of measures in each of the two groups, and we will use an unpaired t-test to compare the mean NPRS-%AUC for patients before and after the intervention.

Percent change in PSEQ-2, PCS-4, CPAQ-8, ODI, SF-12 and total opioid usage (measured in MME) will be compared between groups using ANOVA, or, if more appropriate, a nonparametric Kruskal-Wallis test.

Covariates in the analysis of covariance models include study site, sex, duration of pain, opioid use, and baseline outcome scores.

6.8.2 Statistical Power and Sample Size Considerations

Based on practice history, Geisinger will have sufficient intake of patients fitting the inclusion criteria. Our initial recruitment of 126 patients allows for a 20% dropout rate, which should be sufficient to insure a final n = 100 for statistical analysis and is a reasonable over-estimate, based on prior studies, for the actual dropout rate.

6.9 Data Management

6.9.1 Data Collection and Storage

The following data points will be recorded via direct data collection, retrospective EMR review, and/or the Pennsylvania Prescription Drug Monitoring Program (PDMP) database:

- Medical Record Numbers (MRN) (Will not be included in final data set)
- Name (Will not be included in final data set)
- Patient contact information (e.g. phone, email) (Will not be included in final data set)
- Date of birth
- Patient demographics such as gender, race/ethnicity, and BMI
- Medical history relevant to inclusion/exclusion
- Date(s) of clinic visits
- Outcome measures (see section 6.5 for complete list)

The study coordinator(s) will randomly assign study ID numbers in place of MRNs. All study data will be stored on a secure Geisinger Health System server, and hard copy data will be double locked and accessible only to the study investigators. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication. An IRB approved study team member will share the dataset with appliedVR via a secured e-mail.

The EaseVRx devices will collect information related to device usage (i.e. frequency and duration of use, features utilized, completion rates). When connected to WiFi, the devices will automatically and securely transmit de-identified logs of headset usage. This data contains no PHI, is encrypted in transit, transmitted as frequently as every 5 minutes, and stored in appliedVR's secure and compliant cloud environment. Data will be aggregated and sent in a compatible format to Geisinger to be analyzed and cross referenced with patient study ID numbers.

6.9.2 Records Retention

Records of data generated throughout the course of this study shall be retained indefinitely and may be used for future research projects that have been reviewed and approved by the IRB.

7 SAFETY MONITORING

7.1 Adverse Event Reporting

Clinical adverse events (AEs) will be monitored throughout the study. All AEs will be reported to the institutional review board (IRB) regardless of whether they are considered study related. The date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the study PI. In the event of a serious AE (SAE), this will be reported to the Geisinger IRB (GIRB) according to the GIRB guidelines. All other AEs will be summarized and submitted to GIRB during continuing review.

7.2 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study.

No technical difficulties are anticipated in the performance of these studies; the methods in place are similar to other appliedVR product proof-of-concept studies previously conducted in hospital settings, which revealed no adverse events.

The potential risks posed by EaseVRx to the patient are limited, as the EaseVRx does not control any diagnosis or medical decisions and the patient is free to suspend or halt use at any time by removing the VR headset. The primary risk is that the patient does not respond to EaseVRx and continues to feel pain. Other risks include minor adverse events such as motion sickness, vertigo, nausea, vomiting, or panic attacks. Again, these rare adverse events can be remedied by removing the VR headset. EaseVRx includes a wide range of experiences to allow for patients with phobias or triggers for panic attacks to choose other experiences which do not incorporate those factors.

A **serious adverse event** (SAE) is an AE that:

- Results in death.

- Is life-threatening (see below).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below).
- Results in a persistent or significant disability or incapacity (see below).
- Results in cancer.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information. Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article, except for exposure to prenatal vitamins. If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposure are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE.
- Overdose of a test article as specified in this protocol with or without an AE. Baby formula overdoses without any AEs are excluded.
- Inadvertent or accidental exposure to a test article with or without an AE.

7.3 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the informed consent form to the completion of post-treatment outcome measures collection at 3 months.

7.4 Serious Adverse Event Reporting

Dr. Chulhyun Ahn will notify GIRB of all study SAEs in accordance with policy guidelines. If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g. concomitant medication, medical history) will be submitted to GIRB. An SAE will be followed until either resolved or stabilized.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Be allowed to visually and manually inspect the device.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

8.2 Protection of Human Subjects Against Risks

The investigator will provide for the protection of the subjects by following all applicable regulations. Anticipated risks in this study are minimal. The major risk to human subjects is the accidental disclosure of PHI. In this regard, the assignment of a study ID number to each individual participant and the protocol of providing only the necessary associated clinical information to the remainder of the research team will mitigate this risk. All data will be coded and encrypted while being transferred.

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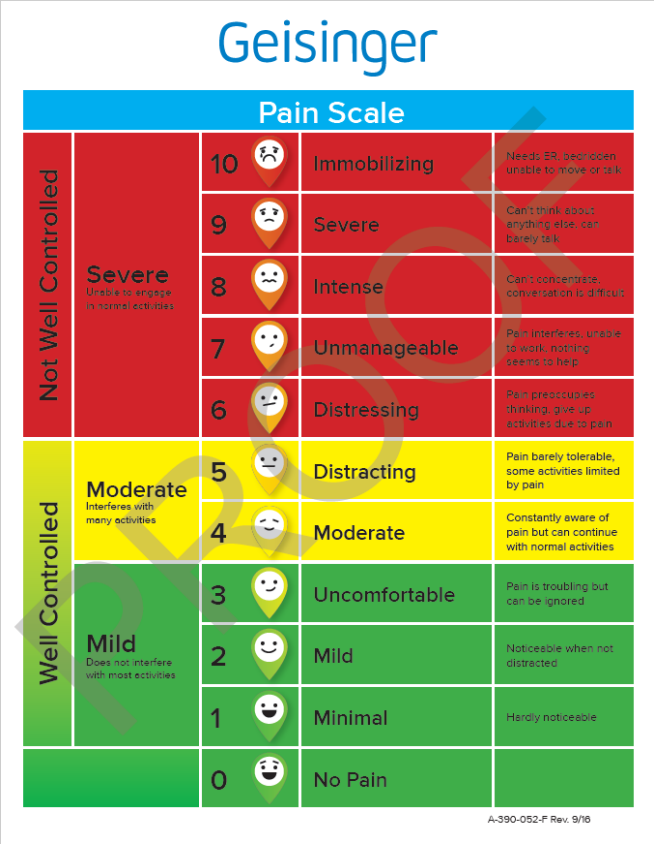
1 ATTACHMENTS

1.1 Attachment 1: Geisinger NPRS Pain Scale



1.2 Attachment 2: PROMIS Pain Interference Short Form 6b

In the past 7 days…

How much did pain interfere with your enjoyment of life?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How much did pain interfere with your ability to concentrate?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How much did pain interfere with your day to day activities?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How much did pain interfere with your enjoyment of recreational activities?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How often did pain keep you from socializing with others?

Never	Rarely	Sometimes	Often	Always
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

1.3 Attachment 3: PROMIS Physical Function 6b

Are you able to do chores such as vacuuming or yard work?

Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Are you able to go up and down stairs at a normal pace?

Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Are you able to go for a walk of at least 15 minutes?

Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Are you able to run errands and shop?

Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Does your health now limit you in doing two hours of physical labor?

Not at all	Very little	Somewhat	Quite a lot	Cannot do
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?

Not at all	Very little	Somewhat	Quite a lot	Cannot do
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

1.4 Attachment 4: PROMIS Global Health Measures

In general, you would say your health is:

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In general, you would say your quality of life is:

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In general, how would you rate your physical health?

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In general, how would you rate your mental health, including your mood and ability to think?

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In general, how would you rate your satisfaction with your social activities and relationships?

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

Excellent	Very Good	Good	Fair	Poor
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?

Never	Rarely	Often	Sometimes	Always
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How would you rate your fatigue on average?

None	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How would you rate your pain on average?

No pain ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst imaginable pain

1.5 Attachment 5: 12-item Short Form Health Survey (SF-12)

1. In general, would you say your health is:

_____ Excellent (1)
_____ Very Good (2)
_____ Good (3)
_____ Fair (4)
_____ Poor (5)

The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

2. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:
_____ Yes, Limited A Lot (1)
_____ Yes, Limited A Little (2)
_____ No, Not Limited At All (3)

3. Climbing SEVERAL flights of stairs:
_____ Yes, Limited A Lot (1)
_____ Yes, Limited A Little (2)
_____ No, Not Limited At All (3)

During the PAST 4 WEEKS have you had any of the following problems with your work or other regular activities AS A RESULT OF YOUR PHYSICAL HEALTH?

4. ACCOMPLISHED LESS than you would like:
_____ Yes (1)
_____ No (2)

5. Were limited in the KIND of work or other activities:
_____ Yes (1)
_____ No (2)
During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

6. ACCOMPLISHED LESS than you would like:
_____ Yes (1)
_____ No (2)

7. Didn't do work or other activities as CAREFULLY as usual:
_____ Yes (1)
_____ No (2)

8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?
_____ Not At All (1)
_____ A Little Bit (2)
_____ Moderately (3)
_____ Quite A Bit (4)
_____ Extremely (5)

The next three questions are about how you feel and how things have been DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS –

9. Have you felt calm and peaceful?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

10. Did you have a lot of energy?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

11. Have you felt downhearted and blue?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

12. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

1.6 Attachment 6: Pain Self-Efficacy Questionnaire (PSEQ-2)

A measure of effective coping strategies

1. "I can still accomplish most of my goals in life, despite the pain"

0	1	2	3	4	5	6
Not at all			confident			Completely confident

2. "I can live a normal lifestyle, despite the pain"

0	1	2	3	4	5	6
Not at all			confident			Completely confident

1.7 Attachment 7: Pain Catastrophizing Scale (PCS-4)

Instructions: We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are 4 statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

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

When I'm in pain…

1.	It's terrible and I think it's never going to get better	0	1	2	3	4
2.	I become afraid that the pain may get worse	0	1	2	3	4
3.	I anxiously want the pain to go away	0	1	2	3	4
4.	I keep thinking about how badly I want the pain to stop	0	1	2	3	4

1.8 Attachment 8: Chronic Pain Acceptance Questionnaire (CPAQ-8)

Directions: Below you will find a list of statements. Please rate the truth of each statement as it applies to you by circling a number. Use the following rating scale to make your choices. For instance, if you believe a statement is 'Always True', you would circle the 6 next to that statement.

Never true 0	Very rarely true 1	Seldom true 2	Sometimes true 3	Often true 4	Almost always true 5	Always true 6

1.	I am getting on with the business of living no matter what my level of pain is	0	1	2	3	4	5	6
2.	Keeping my pain level under control takes first priority whenever I am doing something	0	1	2	3	4	5	6
3.	Although things have changed, I am living a normal life despite my chronic pain	0	1	2	3	4	5	6
4.	Before I can make any serious plans, I have to get some control over my pain	0	1	2	3	4	5	6
5.	I lead a full life even though I have chronic pain	0	1	2	3	4	5	6

6.	When my pain increases, I can still take care of my responsibilities	0	1	2	3	4	5	6
7.	I avoid putting myself in situations where my pain might increase	0	1	2	3	4	5	6
8.	My worries and fears about what pain will do to me are true	0	1	2	3	4	5	6