Development and validation of a digital pain-reduction kit for musculoskeletal injuries

Protocol Number: Pro00049015

National Clinical Trial (NCT) Identified Number: NCT03187132

Principal Investigator: Brennan Spiegel, MD

Sponsors: Travelers Insurance, Samsung, appliedVR

Funded by: Travelers Insurance

Version Number: v.6.4

30 August 2019

Original: 22 February 2018

Most recent changes highlighted in yellow

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.2, 5.5, 8.1	EMA added, new Aleve unit contraindications, summary of LBP patient sampling	
1.3,2.2, 4.1, 8.1, 6.1.1, 7.2, 5.1, 2.3.1, 2.3.3, 5.5, 10.1.5	Clarified number of visits, clarified focus on orthopedic injuries, updated sample size for consistency, added language on phone and equipment, modified inclusion criteria for smartphones, added data risks/mitigation, recruitment update, removed Bayer HealthCare from study funding/sponsorship	IRB Approval
4.1, 5.1	Clarified recruitment strategy for LBP	
1.1, 1.3, 4.1, 5.2, 6.1.1, 8.1, 9.1	Change from CG-CAHPS to different patient satisfaction questionnaire, added TENS protocol for all patients, and redefined digitalist physician as clinical health coach	

1.1,2.1, 2.2,5.1,5.2,5.5, 6.1.1,10.1.1.2,	**Change in eligibility with clarifications made in other sections to reflect this change.**	**This will allow patients at new clinical sites to be involved in the study and allow recruitment of LBP patients.**
6.1.1	**Change in technology used to display audiovisual content for the patient.**	**The new technology will be far easier for the patients to use at home.**
5.5, 8.1	**Specific letters provided to patients, addition of Redcap as a method to collect PROs**	**For the patients comfort a letter tailored to the treating provider will be added, Redcap was added to increase the number of ways patients could provide PROs.**
6.1.1	**PICO G2 added as another VR headset that patients may receive.**	**An update to the Oculus software rendered the intervention software inoperable. The software vendor has started to use a different but comparable VR headset. The headset they are using is called the PICO G2. It will have the exact same software provided to the patient as what was provided via the Oculus Go.**
1.1, 5.5	Medical College of Wisconsin (MCW) added as fourth screening and enrollment site.	The study is now multi-site with the addition of Medical College of Wisconsin (MCW) to accelerate recruitment rates.
9.2	Increased total sample size to 145	A greater number of patients are required to maintain statistical power due to an unanticipated number of withdrawals due to low survey compliance.

Table of Contents

STATEMENT OF COMPLIANCE

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

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

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

The protocol, informed consent form(s), recruitment materials, and all participant 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.

1 PROTOCOL SUMMARY

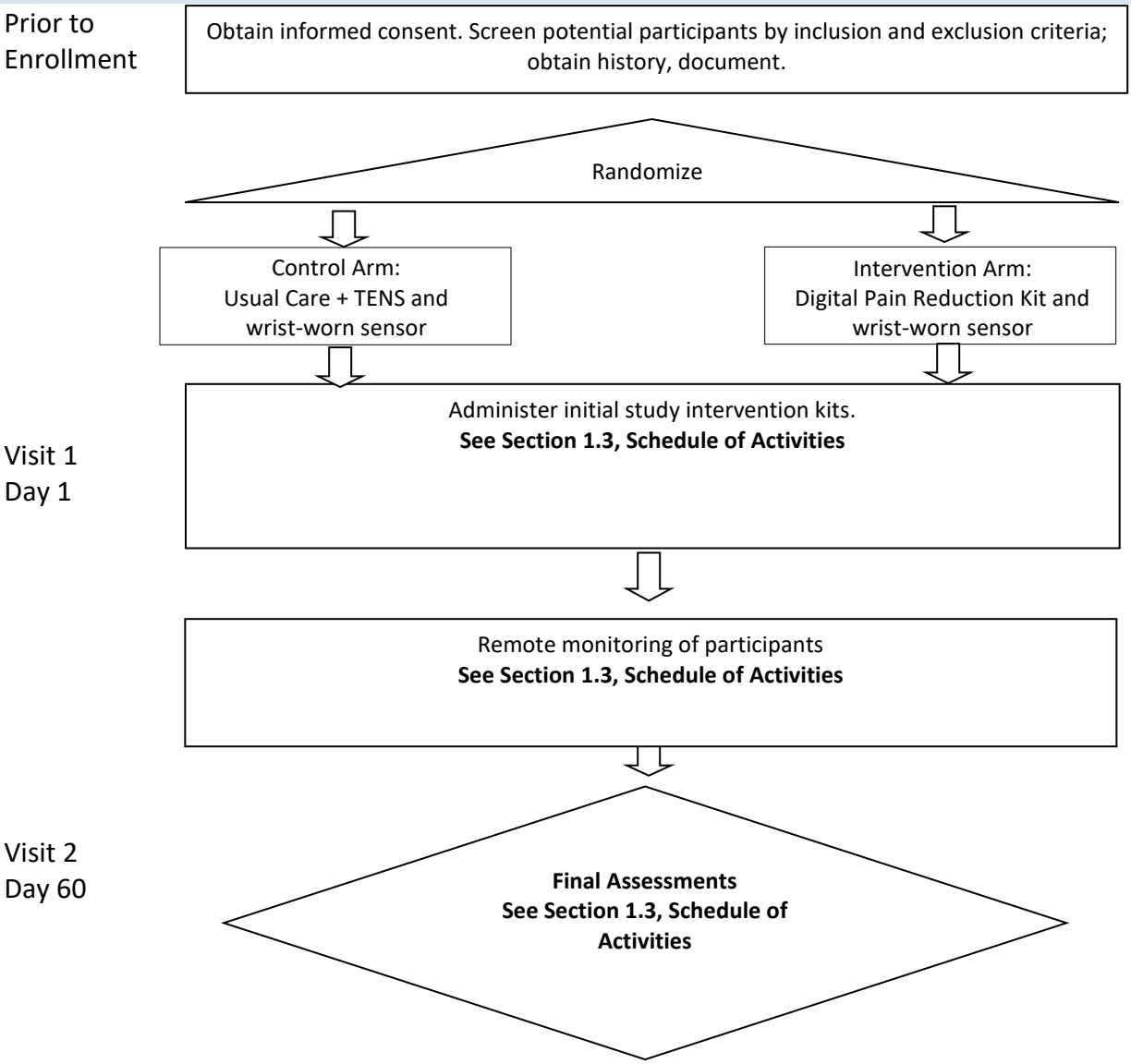
1.1 SYNOPSIS

Title:	Development and validation of a digital pain-reduction kit for musculoskeletal injuries
Study Description:	This study will test the effectiveness of an evidence-based, multi-modal, "digital pain-reduction kit" as a non-pharmacological supplement to managing patients with pain due to musculoskeletal injuries. Outpatients will be randomized to receive either the pain reduction kit or an active control. The kit will contain a virtual reality (VR) headset, therapeutic VR visualization software, a low-cost wearable transcutaneous electrical nerve stimulation (TENS) unit. The control group will receive a TENS unit; they will not receive VR, or remote coaching. Study devices will be delivered to the patient's home with instructions for use; patients will receive remote clinical and technical support. Patients will be followed for 60 days and monitored for functional status, pain levels, use of pain medications (including opioids), satisfaction with care, and time to returning to work. Participants will also be asked to consent/authorization to access medical records from their treating facility (if a non-CSMC site).
Objectives:	Primary Objective: The primary objective of this study is to develop and validate a multi-modal digital pain reduction kit for improving physical function over time. Secondary Objective: The secondary objective of this study is to investigate the efficacy of a multi-modal digital pain reduction kit in reducing pain interference over time, work productivity, opioid use, and satisfaction with care.
Endpoints:	Primary Endpoint: The primary outcome measures in this study are weekly surveys (PROMIS® PF short-form) of self-reported physical function. Secondary Endpoints: The secondary outcome measures in this study are pain interference (PROMIS® Pain Interference), work absenteeism and presenteeism (WPAI:LB), number of 90 Morphine Milligram Equivalent opioid prescriptions, and satisfaction with healthcare (Pain Treatment Satisfaction Scale and SF Patient-Satisfaction Questionnaire).
Study Population:	The study consists of 174 English adults (75 intervention; 75 control with TENS; 24 control without TENS) in the Greater Los Angeles Area presenting with pain from musculoskeletal injuries.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Cedars-Sinai Medical Center Orthopedic Clinic Cedars-Sinai Medical Delivery Network (MDN) Medical College of Wisconsin (MCW)
Description of Study Intervention:	Participants assigned to the control arm will receive standard of care, TENS unit. Participants assigned to the intervention will receive standard of care, plus the following study components: - Virtual reality headset with integrated video experiences (3x daily)

- Transcutaneous electrical nerve stimulation unit for pain reduction (used as needed)
- Remote clinical and technical support (opt-in, then health coach-initiated)

Study Duration: 16 months
Participant Duration: 60 days

1.2 SCHEMA


Prior to Enrollment
Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Control Arm:
Usual Care + TENS and wrist-worn sensor
Intervention Arm:
Digital Pain Reduction Kit and wrist-worn sensor
Visit 1
Day 1
Administer initial study intervention kits.
See Section 1.3, Schedule of Activities
Remote monitoring of participants
See Section 1.3, Schedule of Activities
Visit 2
Day 60
Final Assessments
See Section 1.3, Schedule of Activities

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -7 to -1	Visit 1, Day 1	Day 7 +/-1 day	Day 14 +/- 1 day	Day 21 +/-1 day	Day 28 +/-1 day	Day 35 +/-1 day	Day 42 +/-1 day	Day 49 +/-1 day	Day 56 +/-1 day	Final Study Visit 2 Day 60 +/-1 day
Informed consent	X										
Demographics	X										
Medical history	X										
Randomization	X										
EHR data (opioid use)		X									X
Administer study intervention kits		X									
Intervention (Virtual reality)		X	X	X	X	X	X	X	X	X	X
Intervention (TENS)		X	X	X	X	X	X	X	X	X	X
PROMIS® questionnaires		X	X	X	X	X	X	X	X	X	X
Assess absenteeism and presenteeism (WPAI)		X									X
Satisfaction with pain treatment and healthcare											X
Collect VR compliance data		X	----------								X
Remote clinical and/or technical support		X	----------								X
Collect study intervention kits											X

Note: Participants will only have two site visits, the SoA illustrates additional days for remote measurement. Site visit days are labeled as "Visit 1" and "Visit 2."

2 INTRODUCTION

2.1 STUDY RATIONALE

The aim of this randomized, controlled trial (RCT) is to assess the relative benefits of using a digital pain-reduction kit (including virtual reality unit, transcutaneous electrical nerve stimulation unit, and remote clinical support) for pain management outcomes – including functional status, pain interference, work productivity and activity impairment, usage of pain medication, and satisfaction scores in a cohort of patients with pain related to musculoskeletal injuries.

2.2 BACKGROUND

Pain from musculoskeletal injuries is a prevalent and expensive condition that negatively impacts health related quality of life (HRQOL), diminishes functional status, and leads to a high rate of work absenteeism. Some patients with musculoskeletal injuries, including lower back pain, turn to opioids, a class of medications that may provide effective analgesia but can lead to opioid use disorder, opioid-related overdoses and serious adverse events, including death. The average time lost for workers using opioids can total as much as $117,000 per insurance claim – a value that is 900% higher than the cost of claims for workers who do not take opioids. From both a clinical and health economic perspective, it is vital to identify opioid-free treatments to assist in the management of pain caused by musculoskeletal injuries.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Short-term risks associated with the study may include minor psychological distress from questionnaires regarding health and employment status, acute virtual reality discomfort (e.g., headache, vertigo, nausea), and minor side effects from transcutaneous electrical nerve stimulation (e.g., muscle twitching, muscle soreness, skin irritation).
There are no anticipated long-term risks from participating in this study.
Participants may elect to receive standard of care in lieu of participation in the study.
There are some risks associated with the electronic collection and transmission of protected health information for the purpose of research. Unanticipated breaches of data may result in exposure of confidential information to individuals outside of study staff.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential immediate benefits include reduction of pain due to musculoskeletal injuries and global improvements in psychological health. Potential long-term benefits include improved functionality and work productivity, reduced opioid use, and improves in global physical health.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The TENS unit is an FDA-approved over-the-counter consumer-grade device and is contraindicative in women who are pregnant. Pregnant women were excluded from the study to minimize risk from the TENS unit. Virtual reality hardware and software has advanced significantly this decade and sophisticated motion tracking eliminates helps to minimize discomfort among participants. Modern studies utilizing VR have found general satisfaction with devices among participants. Still, individuals with neurological disorders or hypersensitivity to lights were excluded to minimize risk from VR exposure. 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.
To minimize risk of breaches in confidentiality associated with the access and recording of protected health information, study staff will be assigned unique passwords and usernames to access secure servers. Additionally, identifiable information for participants will be obfuscated using unique ID numbers and a linking list will be held in a secure location.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is to develop and validate a multi-modal digital pain reduction kit for improving physical function over time.	The primary endpoint in this study is a clinically significant change in self-reported physical function over time among individuals in the intervention arm compared to those in the active control. The outcome measure used to quantify this endpoint is the PROMIS® PF short-form, a validated self-report of physical function. The	The PROMIS® PF short-form scale is a widely validated instrument with excellent content validity, construct validity, and reliability in patients with spinal disorders and other conditions marked by

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	outcome measure is administered on a weekly basis via a smartphone survey to capture longitudinal change and variation among participants.	diminished mobility. The outcome measure allows us to place patients on a continuum of physical function with respect to various physical actions.
Secondary		
The secondary objective of this study is to investigate the efficacy of a multi-modal digital pain reduction kit in reducing pain interference over time, work productivity, opioid use, and satisfaction with care.	The secondary endpoints of are clinically significant changes in pain interference, work productivity, use of opioids, and satisfaction with healthcare among those in the intervention arm compared to participants in the active control. Outcome measures include pain interference (PROMIS® Pain Interference, measured weekly via smartphone surveys), work absenteeism and presenteeism (WPAI:LB, measured at baseline and exit surveys), number of 90 Morphine Milligram Equivalent opioid prescriptions (obtained via cumulative EHR records), and satisfaction with healthcare (CG-CAHPS, measured once at the conclusion of the study).	
Tertiary/Exploratory		
N/A	N/A	N/A

4 STUDY DESIGN

4.1 OVERALL DESIGN

This RCT will enroll 174 patients with pain due to musculoskeletal injuries to test the efficacy of a multi- model digital pain reduction kit on short term pain management as an adjunct to traditional medical therapy. We will attempt to enroll a minimum of 90 patients reporting lower back pain specifically, as patients without lower back pain are less likely to use the TENS unit. Prior to adding the TENS unit to the control arm, we recruited 24 control patients. However, we will not discard their data since we intend on performing a supplementary sensitivity analysis. In addition to these 24 controls, we will randomize 75 patients to receive the study intervention (multi-modal digital pain-reduction kit with optional remote coaching support), and the other 75 patients will receive an active control. We will allocate patients using a random number generator to ensure that there is an equal distribution of participants in the control vs. experimental group. The primary outcome will be changes in self-reported physical function measured by the Patient Reported Outcome Measurement Information System (PROMIS®) Physical Function Scale. Secondary outcomes will include PROMIS® Pain Interference Scale, PROMIS® Global Health Scale, work productivity and activity impairment questionnaire (WPAI) (for patients with lower back pain specifically), patient satisfaction measured by the Pain Treatment Satisfaction Scale and SF Patient-Satisfaction Questionnaire), and use of opioids (measure in morphine milligram equivalents).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The active control group in the randomized control trial minimizes biases related to reactivity administering standard care of care in addition to a passive measurement component. Therefore, the control group may show some effect and limit the effect size of the intervention, given that TENS units have been shown to reduce pain, at least in the short term.

4.3 JUSTIFICATION FOR DOSE

The TENS unit and VR are to be used as needed during patient flares of pain. The three daily doses are a recommendation and patients may deviate as necessary contingent on their pain levels.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all components of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 or older
4. Seeking care for a musculoskeletal injury
5. Experiencing pain greater than 3 out of 10 on a visual analog scale
6. English speaking
7. Owns a compatible Android or iOS smartphone device (excluding tablets)

5.2 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. Pregnant (contraindication for TENS unit)
3. Use of a cardiac pacemaker, implanted defibrillator, or other implanted metallic or electronic device or high frequency surgical equipment. (contraindication for TENS units)
4. Current diagnosis of epilepsy, dementia, or other neurological disease that may prevent use of VR hardware or software
5. Hypersensitivity to flashing light or motion
6. Injury to the eyes, face, neck, or arms that prevents comfortable use of VR hardware or software, or safe use of other study hardware (e.g., open sores, wounds, or skin rash on face)

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. 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).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a will not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Male and female participants above the age of 18 will be screened to reach target enrollment 174 patients over a period of 16 months. Participants presenting with pain due to a musculoskeletal injury will be screened and enrolled at four sites (Cedars Sinai Orthopedic Clinic, Medical Delivery Network, Cedars Sinai Pain Management Clinic, Medical College of Wisconsin). Patients will be identified and approached by their providers. The treating physicians will contact their patients during their clinic visits and assess the patient's willingness to be contacted about the research and the treating physician will document the patient's willingness to be contacted on the *CSMS Research Interest* letter. The Research Letter will be tailored to each clinical practice of the treating provider. Additionally, participating providers will distribute recruitment pamphlets to patients in clinic and/or through mail. Should the patient be interested in being contacted about the study, the study team will then approach the patient for

participation in the research either in person or over-the-phone. The patient will have the option to complete their consent forms on paper or electronically using the 21 CFR 11-compliant online platform, DocuSign. Every subject will be informed of the approximate time to complete the consent process. Consenting will be done with a research staff member either in-person or remotely via DocuSign to ensure the identity of the person signing the informed consent form is indeed the subject participating in the research study. A copy of the informed consent documents will be given to the participants for their records via their email or a physical hard copy. Participants who consent remotely will receive their study equipment through a secure FedEx package requiring a signature. Retention to the 60-day study for the intervention group will be managed using weekly reminders to complete survey protocols, as well as optional opt-in monitoring of compliance and health data via remote clinical and technical support staff. Participants will not receive monetary compensation for participating in this study.

Participants experiencing lower back pain will be oversampled to a minimum of 45 per arm in order to obtain sufficient sample size for testing the success of the TENS unit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Study Intervention: Digital Pain Reduction Kit

The study intervention will include evidence-based digital devices that offer non- pharmacological solutions to managing pain. Patients in the intervention group will receive access to two devices: (1) Oculus Go headset or PICO G2 headset with preloaded therapeutic visualization software developed by appliedVR; (2) Aleve® Direct Therapy TENS Device. Study staff will monitor patient progress remotely and provide guided support and coaching. The sections, below, describe the components of the intervention.

Smartphone, VR Headset, and Software

To care for the whole patient, clinicians must consider not only the physical impact of illness, but also the psychosocial impact. However, the dynamic nature of clinical medicine, coupled with limited time to spend with individual patients, pose challenges to offering holistic care for patients with pain.

Treatment of pain is often focused on pharmacological management which can yield inconsistent and sub-optimal pain control.[2] However, extensive data reveal that adjunctive non-pharmacological techniques, such as cognitive behavioral therapy and relaxation techniques, can modify cognitions and behaviors that influence the perception of pain.[3] VR technology provides an immersive, multisensory, and three-dimensional (3D) environment that enables users to have modified experiences of reality by creating a sense of “presence”.[4 5] To date, VR has been used in numerous clinical settings to help treat anxiety disorders, control pain, support physical rehabilitation, and distract patients during wound care.[4-12] For example, VR coupled with medication is effective in decreasing pain during bandage changes for severe burns.[6 10 13 14] Similarly, VR reduces pain and provides positive distraction during routine procedures, such as intravenous line placements[9] and dental procedures.[7 15] Other studies reveal that VR helps manage chronic pain conditions such as complex regional pain syndrome[16] and chronic neck pain.[17] Our own research shows that VR can reduce pain by an average of 24% among hospitalized patients with a wide

range of somatic and visceral pain. By stimulating the visual, auditory, and proprioception senses, VR acts as a distraction to limit the user's processing of nociceptive stimuli.[5]

However, despite the evidence and increasing media attention surrounding VR, there have been no controlled trials using VR at scale to manage outpatient musculoskeletal pain, particularly low back pain (the most common reason for worker compensation claims and lost productivity).

This RCT will use a Oculus Go or PICO G2 all in one head mounted display that delivers VR images and sound. We selected the Oculus Go and PICO G2 because they are commercially available, widely used, inexpensive, have minimal visual latency, and are much easier for patients to use than devices used in our previous research. [18] Higher end tethered headsets, such as the Oculus Rift, are currently more expensive and onerous to use at scale in an inpatient setting.

Users will wear the VR goggles. Detailed instructions will familiarize patients with hardware; and telephonic and email technical support from study staff will be available to advise patients having trouble using the equipment. Patients unable to use the device at home will be offered an in-person visit with study staff to troubleshoot and train.

We will use the appliedVR app to offer >30 therapeutic VR experiences through the headsets. Our team has worked with appliedVR to curate experiences that are acceptable to a wide range of patients. The app includes a menu of visualizations, each mapped to a therapeutic benefit (e.g. pain reduction, anxiety reduction, mindful meditation).

The app includes "Pain RelieVR", a 15-minute VR experience specifically designed to treat pain in patients with limited mobility. Pain RelieVR is an immersive, 360-degree game experience that takes place in a fantasy world where the user attempts to shoot balls at a wide range of moving objects by maneuvering their head towards the targets. This engaging, medium-intensity activity is free of interruption, offering the user a distracting experience designed to reduce the perception of pain. Pain RelieVR is a non-violent and non-competitive game that incorporates motivational music and features positively reinforcing sounds, animation and direct messages to patients. Forward- facing action allows patients with limited mobility to engage without having to turn backwards or contort into potentially uncomfortable positions.

The app also includes "Anxiety RelieVR," an interactive, meditative landscape along a peaceful shoreline . In contrast to Pain RelieVR, which acts through distraction therapy, Anxiety RelieVR employs mindful meditation to help manage the affective component of pain. These cornerstone experiences are supported by a wide range of additional therapeutic journeys, including an Iceland flyover in a helicopter, an undersea experience, and a variety of nature-related experiences, among many others.

Patients can pick and choose which visualizations to watch based on their own preferences. In clinical testing, we asked patents to use the headset at least thrice daily, for 10 minutes per treatment period, and to also use as needed for breakthrough pain between treatments. The appliedVR software allows our team to monitor adherence with the therapy, including the visualizations selected by the user, the amount of exposure time, and the time of day the visualization was viewed.

TENS Device

We will supplement therapeutic VR with TENS, another evidence-based, non-invasive, non-pharmacological pain reduction technique. TENS employs an electric current to stimulate nerves in a manner thought to release intrinsic endorphins and to block transmission of nociceptive signals. Data measuring brain function with evoked cortical potentials and functional magnetic resonance imaging (fMRI) suggests that TENS may suppress pain signals centrally, in addition to its direct peripheral benefits on the sensory nerves. Although clinical evidence is inconsistent among studies, types of pain (chronic vs. acute), and location of pain, TENS units have been FDA cleared as a class II device for many years, and consumer satisfaction with these devices is consistently high.

Clinical data reveal benefits of TENS for lower back pain. In a recent meta-analysis of RCTs, cohort studies, and randomized crossover studies for TENS in lower back pain, Jauregui and colleagues determined the technique significantly reduces pain intensity, particularly for short term treatment (<5 weeks).[19] The authors concluded that TENS may lead to less pain medication usage and should be incorporated into the treatment armamentarium for low back pain.

For this study, we will use an over-the-counter, consumer-facing product called the Aleve Direct Relief TENS Device. This device is designed for use over the lower back for management of pain of lumbosacral origin. Treatment periods last 30 minutes and include three stages. In stage I, the device emits 5 minutes of high frequency stimulation (>50 Hz) to initiate anti-nociceptive effects through diminished processing of pain signals. In stage II, the device emits 20 minutes of low frequency stimulation (<20 Hz) to release endorphins as a second mechanism of pain reduction. The treatment period ends with stage III, in which another 5 minutes of high frequency stimulation is deployed with the aim of maintaining the initial pain relief established by phases I and II. Patients receive a handheld remote control to adjust the intensity of the electrical stimulation based on personal preference and tolerance. The device is used as needed for breakthrough pain, or as baseline prophylactic treatment.

Clinical and Technical Support

Patients in the intervention arm will not only receive the digital pain reduction kit, but also will receive remote technical and clinical support from the research team. The idea is that issuing devices is usually insufficient to achieve behavior change; supporting those device with high-touch yet scalable care is a vital component.

Rationale for "Digitalist" Model of Remote Clinical Monitoring

Integrating digital technologies into a harmonized health delivery model may improve process and outcomes of care. If used effectively, digital health monitoring may tailor care to individual patients, extend clinicians' reach outside of the hospital and clinic, improve timeliness and specificity of care, deliver proactive (not reactive) care, and better engage patients in their health.[20]

Still, there are important questions we need to answer: Who will be checking all the data? How can doctors, who are busy in the clinical trenches, be responsible for monitoring and acting upon the data streaming off wearable sensors, apps, and patient-provider portals? Who has time for this? The reality is that no doctor has enough bandwidth to check mobile health (mHealth) data on a regular basis. Clinicians are too busy for this work.[20]

One answer for moving digital health forward is to develop a new type of specialist called the "Digitalist."[20] The Digitalist does not yet exist at scale, just as "The Hospitalist" did not exist prior to 1996, when Robert Wachter and Lee Goldman coined the term to describe a much-needed clinician to fill an unmet need for inpatient care.[21] Now we have an unmet need for a new clinician (though not necessarily a physician), trained in digital health, who will monitor, interpret, and act upon remote patient data – in this instance among patients recovering from a low back injury. In this study, a health coach, acting similar to a Digitalist, will remotely track data from biosensors, portals, and apps, then combine the data to provide guidance with adhering to the intervention.

Patients transmit actively and passively collected data through apps and portals. The Digitalist monitors the data, and, if needed, contacts the patient via EHR portal, telephone, or videoconferencing. If appropriate, the Health Coach communicates directly with clinicians, informs them of updates, and coordinates the optimal timing of in-person visits. The clinician may also access digital health reports, review the results with the patient, and make further decisions based on the data coupled with the traditional history and physical examination.

This model has potential to expand care beyond the traditional clinic visit, uses visits more effectively, reduces avoidable admissions, and improves outcomes of care.

Implementation of Health Coach Model in Intervention Arm

In the current study, we will simulate aspects of the Health Coach model by allowing patients in the intervention arm to remotely share their secure mHealth data with selected members of the research team. VR usage data will also be transmitted remotely through the appliedVR app, allowing our team to monitor adherence with the VR intervention. We will assign two staff to monitor patients in the control arm: (1) technical support staff member, and (2) Health Coach. Patients will receive a telephone number and email to contact support staff as needed. The technical support staff will also reach out if there is low adherence with the devices, prolonged missing wearable data, or low battery power detected on the remote monitoring dashboard. The Health Coach will reach out if there is evidence of worsening physiologic or activity parameters (e.g. walking less, sleeping less, heart rate increasing) using their clinical judgment. Patients will be informed to contact 911 and/or call their physician directly if they experience any urgent, semi-urgent, or concerning signs or symptoms. The Health Coach will check mHealth data logs twice weekly on weekdays, and contact the patient by phone according to the patient's stated preferences. Patients who do not want Health Coach remote monitoring will not receive this component of the intervention but will still be included in the intention-to-treat population.

6.1.2 DOSING AND ADMINISTRATION

Participants are assigned TENS devices and VR to be used as needed. Participants are also instructed to use VR at least three times a day. The dosage for both devices will not change throughout the study. Individuals assigned to remote monitoring will be continuously monitored and any action will be physician-initiated. Participants in the control group will receive standard of care and TENS unit.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Per the new protocol, participants will be randomized intervention or control until intervention and control groups each have 75 enrollees. In addition to these 150 participants, the group of 24 controls that were originally recruited without the TENS unit will remain accounted for in the supplementary analysis. There will be no blinding, as participants in the control group will be aware that they are missing components of the intervention as detailed in the consent form.

6.3 STUDY INTERVENTION COMPLIANCE

Compliance to the protocol will be monitored using software for the VR modules and remote data uploads of survey logs.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be recorded are concomitant prescription medications, over-the-counter medications, and supplements.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the use of the digital pain reduction kit does not mean 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 reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- 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

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

Participants will not be financially responsible for damage to, or loss of, equipment loaned to participants by investigators during this study.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to comply to weekly surveys, misses exit appointment, and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for the final study visit:

- The site will attempt to contact the participant and reschedule the exit appointment and counsel the participant on the importance of maintaining the assigned visit to return equipment and debrief (whether or not the participant chooses to complete exit surveys).
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

PROMIS® Questionnaires

The primary outcome for this study will be self-reported physical function (PF) using the PROMIS® PF short form scale. For patients with acute pain, PF is often diminished and patients seek return to normal function. The PROMIS® PF short-form scale is a widely- validated instrument with excellent content validity, construct validity, and reliability in patients with spinal disorders and other conditions marked by diminished mobility. The instrument place patients on a continuum of function from extremely low to very high across activities that require physical actions, ranging from self-care to more complex activities that require a combination of skills. The scale is rendered using a T-statistic, where a score of 50 represents the population mean, and 10 points is a standard deviation (SD). The minimally clinically important difference (MCID) on the PROMIS® PF short form is 2 points, or 0.2 SD. [22]

Secondary outcomes will include the PROMIS® pain interference scale and the PROMIS® global health scale. The pain interference scale measures the consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The PROMIS® global health scale is an overall evaluation of one's physical and mental health. We will include this instrument to address outcomes that are not often addressed in pain interventions, including fatigue and mental health. All PROMIS® measures use a 7-day recall period reflecting the previous week's health status.

To collect the patient reported outcomes (PROs) for this study, we will use ecological momentary assessment (EMA) software (LifeData), a HIPAA-compliant, cloud-based survey administration platform capable of administering surveys in real-time. We will also allow patients use Redcap as an alternative program to collect PROs. With this program the patient doesn't have to use an app on their phone and instead just respond to surveys sent to their email address. To administer PROs, we will upload a list of patient email addresses into their HIPAA-compliant website which in turn allows scheduled administration of PRO questionnaires at daily and weekly intervals. Each week, the EMA app will send patients a reminder to fill out the scheduled PROs. If they do not fill them out, they will be sent a reminder prompt. The data collected by LifeData or Redcap will then be downloaded into a secure analysis and visualization file accessible to the research team and the Digitalist.

Work Productivity and Activity Impairment

Work productivity can be measured in terms of absenteeism (missing work) and presenteeism (diminished productivity at work). The Work Productivity and Activity Impairment (WPAI) questionnaire is a validated, widely used, brief, 6-item questionnaire that measures absenteeism and presenteeism related to specific health conditions.

Use of Opioids

In order to capture medication use related to their injury, including the use of opioids, we will link patient electronic health record (EHR) data to the other data sources using Medical Record Numbers and date of birth. We will collect opioid prescription information using pharmaceutical claims data, and also collect information on medications commonly used by individuals with chronic pain conditions. Prescribed opioid medications include: codeine, dihydrocodeine, tramadol, morphine, hydromorphone, oxymorphone, tapentadol, buprenorphine, methadone, oxycodone, fentanyl, remifentanil. We will convert all opioid doses into a single metric using morphine milligram equivalents (MME).

Satisfaction with Pain Treatment and Healthcare Surveys

We will evaluate patient experience data as measured by the 39-item Pain Treatment Satisfaction Scale and the 18-item short-form version of the Patient-Satisfaction Questionnaire. Both questionnaires are validated for use in studies to compare patient satisfaction between different treatment assignments.

Use and satisfaction with the TENS device will be monitored via daily questionnaires administered by either LifeData or Redcap (as described above).

8.2 SAFETY AND OTHER ASSESSMENTS

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Primary Outcome: Physical function over time as measured by PROMIS PF score (T- Scored, Continuous)

Question: Which intervention is more effective in improving physical function?

Independent variable of interest: Comparator received, intervention vs. control (Dichotomous)

Potential Covariates: Age, gender, race, ethnicity, mental health comorbidities, chronic pain diagnosis, use of other pain medications (neuropathic pain medications, NSAIDS, antidepressants), benzodiazepine use, number of office visits during study period, baseline PROMIS® scores, encounter month, physician years of practice, physician gender.

- Secondary Efficacy Endpoint(s):

Secondary Outcome: Pain over time as measured by PROMIS Pain Interference Score (T-Scored, Continuous)

Question: Which intervention is more effective in improving patient's pain interference?

Independent variable of interest: Comparator received, intervention vs. control (Dichotomous).

Potential Covariates: Same as Primary Aim.

Secondary Outcome: Effects of lower back pain symptom severity on work productivity and regular activities over time as measured by WPAI:LB (T-Scored, Continuous).

Question: Which intervention is more effective in improving patient's work productivity and participation in regular activities?

Independent variable of interest: Comparator received, intervention vs. control (Dichotomous).

Potential Covariates: Same as Primary Aim.

Secondary Outcome: New Opioid Prescription over 90MME (Dichotomous)

Question: Which intervention is more effective in reducing opioid prescriptions of 90 Morphine Milligram Equivalents (MME) or greater?

Independent variable of interest: Comparator received, intervention vs. control (Dichotomous).

Potential Covariates: Same as Primary Aim.

Statistical Analyses: As in the primary aim analyses, we will employ mixed effects models featuring both fixed effects and random effects to account for within subject variation.

Because this particular outcome is binary, we will use mixed logistic regressions in which the log odds of the outcomes are modeled as a linear combination of the predictors.

Secondary Outcome: Satisfaction with Pain Treatment and Healthcare Scores

Question: Which intervention is more effective in improving how satisfied patients feel with their care?

Dependent variable: Pain Treatment and Patient Satisfaction Scores

Independent variable of interest: Comparator received, intervention vs. control (Dichotomous)

Potential Covariates: Same as Primary Aim.

9.2 SAMPLE SIZE DETERMINATION

We will power this study to detected a 0.6 standard deviation (SD) effect size in PROMIS® PF scores between arms – a value that is three-times the established minimal clinical important difference of 0.2 SD and is considered a "moderate effect" using the

rules of Cohen. Assuming an 80% power, a level of 0.05, and a 25% withdrawal rate, we calculate a minimal
sample size requirement of approximately 120 per arm, for a total of 245 patients.

9.3 POPULATIONS FOR ANALYSES

All randomized participants will be included in the dataset (ITT).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Checks of assumptions underlying statistical procedures will be performed and all corrective procedures will be applied as necessary.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Statistical Analyses: Data for Aim 1 are repeated-measures data and will not support bivariate analysis by Pearson and/or Spearman correlations, as autocorrelation can cause transient or spurious relationships with high correlations for some periods and none for others. Similarly, for a linear regression model, this type of data may cause residuals for the same individual to be correlated. Therefore, we will employ linear mixed models featuring fixed effects and random effects (i.e. random intercepts) to account for within subject variation. We will also perform a differences-in-differences analysis comparing change between baseline and the end of the intervention to determine which strategy resulted in greater improvement in PF.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Statistical Analyses: As in the primary aim analyses, we will employ linear mixed models featuring fixed effects and random effects to account for within subject variation. We will also perform a differences-in-differences analysis comparing change between baseline and the end of the intervention to determine which strategy resulted in greater improvement in PF.

Statistical Analyses: As in the primary aim analyses, we will employ linear mixed models featuring fixed effects and random effects to account for within subject variation. We will also perform a differences-in-differences analysis comparing change between baseline and the end of the intervention to determine which strategy resulted in greater improvement in PF.

Statistical Analyses: In addition to unadjusted comparisons, we will employ multiple linear regression models.

9.4.4 ACCOMODATING ADDITION OF TENS UNIT TO THE CONTROL ARM

An ITT analysis "Includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol."[ref] Accordingly, we will follow the original analysis plan described above with regard to analyzing results by study-arm. In addition to the ITT analysis, however, we will conduct a sensitivity analysis by repeating the statistical procedures in a per-protocol fashion wherein the members of the control arm who did not receive a TENS unit will be dropped from the sample. Directions, magnitudes, and significance of treatment effects will be presented for both analyses.

Furthermore, because the TENS unit will appear in both study arms - and unevenly in the control arm – we recognize that an ITT analysis strictly *by* study-arm risks misidentifying the effect of treatment, while a per-protocol analysis risks introduction of bias. Therefore, we will conduct an additional linear mixed model regression analysis using a term for the TENS that captures the effect of the TENS separately from the effects of study-arm assignment. The model used to fit these data is as follows:

$$\hat{y}_{it} = \beta_0 + \beta_1 time_{it} + \beta_2 study\_arm_{it} + \beta_3 TENS_{it} + e_{it}$$

where time represents change in time from baseline, study_arm indicates status as a control or experimental participant (0= control and 1=experimental), *i* is the individual participant, and TENS indicates TENS unit usage (0= no TENS unit and 1=TENS unit). We can therefore write a regression equation describing each type of patient differentiated by the addition of the TENS unit to control conditions:

Treatment:

$$\hat{y}_{it} = \beta_0 + \beta_1 time_{it} + \beta_2 study\_arm_{it} + \beta_3 TENS_{it} + e_{it}$$

Control w/o TENS:

$$\hat{y}_{it} = \beta_0 + \beta_1 time_{it} + e_{it}$$

Control w/ TENS:

$$\hat{y}_{it} = \beta_0 + \beta_1 time_{it} + \beta_3 TENS_{it} + e_{it}$$

In this manner we isolate the term of interest (study_arm). Given we are only adding one term but 20 subjects, we are comfortable relying on the original power calculation.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The physician will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any delivery of study materials. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 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, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to 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.

10.1.3 CONFIDENTIALITY AND PRIVACY

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

Individuals viewing private and identifiable information, such as physicians, are reasonably expected to be viewing such information whether participants were enrolled in the study. All research activities will be conducted in closed-door, private room during initial contact and subsequent follow-up. The setting for much of the study will be at the participant's discretion, as only two visits (baseline and exit) are made during before and after the intervention period.

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

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

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to Travelers Insurance. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.6 PUBLICATION AND DATA SHARING POLICY

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

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

10.1.7 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 Cedars-Sinai 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.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 PROTOCOL AMENDMENT 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 located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	06/08/2017	Initial Protocol	N/A
1.1	06/19/2017	Minor changes	N/A
1.2	06/25/2017	Changed criteria	Clarification
1.3	07/05/2017	Major changes throughout	IRB review
1.4	07/31/2017	Minor IRB changes	IRB review (round 2)
1.5	02/22/2018	Minor changes to questionnaires , TENS protocol, and health coach definition	Clarification
5.4	10/22/2018	Minor changes to eligibility criteria and other sections reflecting the change	Addition of new clinical site and open recruitment for LBP.
6.1.1	11/12/2018	Change in device used to display the audiovisual content.	The new VR headsets will be far easier for patients to use at home.
6.2	8/7/19	**Specific letters provided to patients, addition of Redcap as a method to collect PROs**	**For the patients comfort a letter tailored to the treating provider will be added, Redcap was added to increase the number of ways patients could provide PROs.**
6.3	8/30/19	**PICO G2 added as another VR headset that patients may receive.**	**An update to the Oculus software rendered the intervention software inoperable. The software vendor has started to use a different but comparable VR headset. The headset they are using is called the PICO G2. It will have the exact same software provided to the patient as what was provided via the Oculus Go.**
6.4	10/4/19	Medical College of Wisconsin (MCW) added as an external study site, and Amit Singh added as an external study team member.	The study is now multi-site with the addition of Medical College of Wisconsin (MCW) to accelerate recruitment rates.

11 REFERENCES

1. Barry Meier BM. The Soaring Cost of the Opioid Economy. Secondary The Soaring Cost of the Opioid Economy June 22 2013 2013. *http://www.nytimes.com/interactive/2013/06/23/sunday-review/the-soaring-cost-of-the-* opioid-economy.html?_r=2&.
2. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. Lancet 2011;377(9784):2226-35 doi: 10.1016/S0140-6736(11)60402-9[published Online First: Epub Date]|.
3. Okifuji A, Ackerlind S. Behavioral medicine approaches to pain. Anesthesiol Clin 2007;25(4):709-19, v doi: 10.1016/j.anclin.2007.07.009[published Online First: Epub Date]|.
4. Malloy KM, Milling LS. The effectiveness of virtual reality distraction for pain reduction: a systematic review. Clin Psychol Rev 2010;30(8):1011-8 doi: 10.1016/j.cpr.2010.07.001[published Online First: Epub Date]|.
5. Li A, Montano Z, Chen VJ, Gold JI. Virtual reality and pain management: current trends and future directions. Pain Manag 2011;1(2):147-57 doi: 10.2217/pmt.10.15[published Online First: Epub Date]|.
6. Carrougher GJ, Hoffman HG, Nakamura D, et al. The effect of virtual reality on pain and range of motion in adults with burn injuries. J Burn Care Res 2009;30(5):785-91 doi: 10.1097/BCR.0b013e3181b485d3[published Online First: Epub Date]|.
7. Furman E, Jasinevicius TR, Bissada NF, Victoroff KZ, Skillicorn R, Buchner M. Virtual reality distraction for pain control during periodontal scaling and root planing procedures. J Am Dent Assoc 2009;140(12):1508-16
8. Garrett B, Taverner T, Masinde W, Gromala D, Shaw C, Negraeff M. A rapid evidence assessment of immersive virtual reality as an adjunct therapy in acute pain management in clinical practice. Clin J Pain 2014;30(12):1089-98 doi: 10.1097/AJP.0000000000000064[published Online First: Epub Date]|.
9. Gold JI, Kim SH, Kant AJ, Joseph MH, Rizzo AS. Effectiveness of virtual reality for pediatric pain distraction during i.v. placement. Cyberpsychol Behav 2006;9(2):207-12 doi: 10.1089/cpb.2006.9.207[published Online First: Epub Date]|.
10. Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ, Furness TA, 3rd. Virtual reality as an adjunctive pain control during burn wound care in adolescent patients. Pain 2000;85(1- 2):305-9
11. Hoffman HG, Garcia-Palacios A, Patterson DR, Jensen M, Furness T, 3rd, Ammons WF, Jr. The effectiveness of virtual reality for dental pain control: a case study. Cyberpsychol Behav 2001;4(4):527-35 doi: 10.1089/109493101750527088[published Online First: Epub Date]|.
12. Morris LD, Louw QA, Crous LC. Feasibility and potential effect of a low-cost virtual reality system on reducing pain and anxiety in adult burn injury patients during physiotherapy in a developing country. Burns 2010;36(5):659-64 doi: 10.1016/j.burns.2009.09.005[published Online First: Epub Date]|.

13. Hoffman HG, Patterson DR, Carrougher GJ. Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: a controlled study. Clin J Pain 2000;16(3):244-50
14. Hoffman HG, Patterson DR, Seibel E, Soltani M, Jewett-Leahy L, Sharar SR. Virtual reality pain control during burn wound debridement in the hydrotank. Clin J Pain 2008;24(4):299-304 doi: 10.1097/AJP.0b013e318164d2cc[published Online First: Epub Date]|.
15. Hoffman HG, Patterson DR, Carrougher GJ, Sharar SR. Effectiveness of virtual reality-based pain control with multiple treatments. Clin J Pain 2001;17(3):229-35
16. Sato K, Fukumori S, Matsusaki T, et al. Nonimmersive virtual reality mirror visual feedback therapy and its application for the treatment of complex regional pain syndrome: an open- label pilot study. Pain Med 2010;11(4):622-9 doi: 10.1111/j.1526- 4637.2010.00819.x[published Online First: Epub Date]|.
17. Sarig-Bahat H, Weiss PL, Laufer Y. Neck pain assessment in a virtual environment. Spine (Phila Pa 1976) 2010;35(4):E105-12 doi: 10.1097/BRS.0b013e3181b79358[published Online First: Epub Date]|.
18. Mosadeghi S, Reid MW, Martinez B, Rosen BT, Spiegel BM. Feasibility of an Immersive Virtual Reality Intervention for Hospitalized Patients: An Observational Cohort Study. JMIR Ment Health 2016;3(2):e28 doi: 10.2196/mental.5801[published Online First: Epub Date]|.
19. Jauregui JJ, Cherian JJ, Gwam CU, et al. A meta-analysis of transcutaneous electrical nerve stimulation for chronic low back pain. Surgical technology international 2016;28
20. Spiegel B. 2015 American Journal of Gastroenterology Lecture: How Digital Health Will Transform Gastroenterology. The American journal of gastroenterology 2016;111(5):624-30
21. Wachter RM, Goldman L. The emerging role of "hospitalists" in the American health care system. The New England journal of medicine 1996;335(7):514-7 doi: 10.1056/NEJM199608153350713[published Online First: Epub Date]|.
22. Hays RD, Spritzer KL, Fries JF, Krishnan E. Responsiveness and minimally important difference for the Patient-Reported Outcomes Measurement Information System (PROMIS) 20-item physical functioning short form in a prospective observational study of rheumatoid arthritis. Annals of the rheumatic diseases 2013:annrheumdis-2013-204053
23. Agency for Healthcare Research and Quality. Principles Underlying CAHPS Surveys. Secondary Principles Underlying CAHPS Surveys 2016. *http://www.ahrq.gov/cahps/about*-cahps/principles/index.html.
24. Rabe-Hesketch S, Everitt BS. A Handbook of Statistical Analysis Using Stata. Fourth Edition ed. Boca Raton, FL: Chapman & Hall/CRC: Taylor & Francis Group, 2016.