Mass General Brigham

Protocol Title: Physical and psychological measures of pain in acute orthopedic injuries: use of at-home virtual reality

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Institutional Review Board
Intervention/Interaction Detailed Protocol

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For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Acute orthopedic musculoskeletal injuries are prevalent and costly. Musculoskeletal injuries (e.g., fractures, dislocations; also known as traumatic injuries) are the leading cause of adult hospitalizations.[1] Many patients develop chronic pain and disability despite recovery of bones and soft tissue.[2] An estimated 1.75 billion people globally have some form of chronic musculoskeletal pain.[3] These patients pose a major public health problem and are costly to the healthcare system due to multiple surgeries and medical appointments.[4]

The care of patients with orthopedic musculoskeletal injuries follows an outdated model that does not address the multifactorial influences on recovery. Catastrophic thinking about pain, pain anxiety, depression are established risk factors for disability and pain in patients with musculoskeletal injuries, regardless of the severity, location or type of injury.[5] Referrals to address the multifactorial influences on recovery are often done after multiple unsuccessful medical procedures (surgery, injections, opioids), when patients have become invested in a medical cure, pain has already become chronic, and treatments are generally less efficacious.

Cognitive-behavioral and mind-body approaches show promise but have limitations. Small to moderate effects have been found for depression, pain bothersomeness, and pain catastrophizing in mixed etiology pain[6,7] including among orthopedic patients.[8,9] The goal of these approaches is to "confront" rather than "avoid" by teaching adaptive coping skills thereby preventing the transition toward chronic pain and disability.[10,11] However, access to these approaches remain poor due to stigma of mental health treatment, reluctance toward psychosocial issues in orthopedic departments, lack of trained providers, health insurance limits, and burdens associated with travel and treatment time.[12,13] Because of the scope of acute orthopedic pain and the national opioid epidemic,[14] there is an urgent need for effective, accessible, low-risk treatments that are acceptable to patients.

Virtual reality (VR) can eliminate barriers to pain management[15] but has not been tested in acute orthopedic patients. Most VR studies have focused on *distraction* to increase pain tolerance limits[16] and provide temporary relief[17] and do not include pain self-management skills training.[18]A recent double-

blind RCT of an at-home *skills-based* VR (*RelieveVRx*) for chronic low back pain found superiority for all primary outcomes (pain intensity, pain-related interference, mood, and stress) and reduced over-the-counter analgesic use versus a immersive VR control.[19] However, there were no changes in several intervention targets (pain catastrophizing, pain self-efficacy, pain acceptance) and clinically important outcomes (prescription opioid use). Additional research is needed to characterize the mechanisms and treatment effects of skills-based VR for preventing chronic pain and disability after acute orthopedic injury.

In this Borsook Project, we propose to conduct the first pilot study of skills-based VR for acute orthopedic injury. We will evaluate the feasibility, signals of improvement, and pain modulation mechanisms of an established skills-based program (*RelieveVRx*) for acute orthopedic injury. *RelieveVRx* is advantageous for this study because it: 1) is FDA-approved for chronic lower back pain but untested in acute orthopedic injury; 2) can be self-administered by patients at-home, 3) is the first to integrate multiple proven behavioral pain management strategies (e.g., education, diaphragmatic breathing, relaxation training, cognition and emotion regulation), 4) is interactive using biofeedback, and 5) the headset collects digital markers of the VR user experience and pain management skills practice. There is immense potential for a VR network modulating system to radically shift our approach to preventing chronic pain and disability as an effective, low-risk non-pharmacological intervention for acute orthopedic injury. If successful, skills-based VR could be easily administered in the clinic or at home, adapted to other pain conditions, and scaled using digital therapeutics.

2. Specific Aims and Objectives

My long-term goal is to evaluate the biopsychosocial mechanisms by which skills-based VR promotes recovery after acute orthopedic injury. Our guiding hypotheses that we will test in subsequent studies is that skills-based regulates autonomic (relaxation), affective (mood and situational anxiety), and evaluative (subjective pain and enjoyment ratings) responses associated with acute pain[16] while also promoting pain self-management skills thus preventing the progression to chronic pain and disability. To accomplish this goal, we will: 1) evaluate a-priori feasibility markers of the self-administered, skills-based, at-home VR program and data collection procedures; 2) explore within-group signals of improvement in multiple measures of pain and pain-related outcomes; 3) identify digital markers of pain modulation induced by skills-based VR to target in subsequent fully-powered trials, and 4) identify signals of tissue blood perfusion and oxygenation on the head using non-invasive Functional near-infrared spectroscopy (fNIRS) during normal extremity movements and while using the VR.

3. General Description of Study Design

My approach follows the NIH Stage Model[20] and NCCIH framework,[21] which specify testing feasibility and identification of putative intervention targets before conducting an efficacy trial.[22–24] We will conduct a mixed-methods feasibility pilot and with individual exit interviews (N=10) following procedures for successful orthopedic behavioral intervention trials from our group.[25,26] Participants will be patients with acute orthopedic musculoskeletal injuries who are at risk for chronic pain and disability (PCS ≥ 20 and PASS-20 ≥ 40) and meet inclusionary/exclusionary criteria. With a trained RA, we will recruit patients from Mass General Brigham Orthopedics Departments (Orthopedic Trauma at MGH and Brigham and Women's Hospital, Sports Medicine Services, Hand & Arm Services) through established partnerships on active trials (~220 patients/year meet criteria) through our IRB-approved study flyer.

The skills-based VR will be self-administered by patients at-home over an 8-week period. The primary outcome for the pilot will be a-priori Go/No-Go feasibility markers (feasibility, acceptability, fidelity, credibility, expectancy, satisfaction) of the VR program and data collection procedures to increase the success of subsequent trials. To inform outcomes and mechanisms of action, we will integrate four quantitative assessment techniques: 1) multi-modal assessment (following IMMPACT criteria for pain trials)[27] of pain intensity, pain-specific coping (catastrophizing, self-efficacy, acceptance), disability, physical function, and emotional function (depression, anxiety, stress); digital markers (VR use data, smartphone pain survey) for tracking dynamics of pain during the 8-week intervention; non-invasive fNIRS placed on the head (tissue blood perfusion and oxygenation) for brain activity during extremity movement and use of VR. Participants will travel to the clinic at baseline to pick up the VR equipment and complete the study assessments (self-reports and non-invasive fNIRS). Participants will return to the clinic after the 8-week intervention to repeat the assessment and drop off the VR. Given that skills-based VR has not been tested in this population, 30 min individual exit interviews will be critical for understanding patients' perception of: 1) the rationale and helpfulness of the skills; 2) the VR user experience; 3) barriers and facilitators to treatment adherence; 4) burden of the study procedures and data collection. The deliverables of this pilot study include: refined study protocol; preliminary feasibility; within-group signals of improvement; assessment of biomarkers; assessment of non-invasive fNIRS tissue perfusion and oxygenation; training in VR and mechanistic-based data collection; subsequent NIH proposal.

4. Subject Selection

4a. Inclusion and Exclusion Criteria

The eligibility criteria is consistent with our IRB-approved intervention study for acute orthopedic injury (protocol #: 2020P000095) and guidelines for VR studies for pain.[12,18,19]

Eligible patients must meet the following inclusion criteria:

1) Outpatient adults in the Level 1 Trauma Center
2) Age 18 or older
3) Able to meaningfully participate meaningfully (English fluency and literacy) and stable living situation
4) Acute upper or lower extremity musculoskeletal injury (e.g., fracture, dislocation, rupture) in the acute phase or repeated injury.
5) Pain Catastrophizing Scale ≥20 or Pain Anxiety Symptom Scale-20 ≥40
6) Has access to internet (Wi-Fi or wireless)
7) Willing to participate and comply with the requirements of the study protocol, including virtual reality program and questionnaire completion
8) Free of concurrent psychotropic medication for at least 2 weeks prior to initiation of treatment, OR stable on current psychotropic medication for a minimum of 6 weeks and willing to maintain a stable dose (i.e., no psychotropics or stable for >6 weeks)
9) Cleared by orthopedic surgeon for study participation

One or more of the following exclusion criteria will render a patient ineligible:

1) Current or prior diagnosis of epilepsy, seizure disorder, dementia, migraines, or other neurological diseases that are contraindicated for VR
2) Medical condition predisposing to nausea or dizziness

3) Hypersensitivity to flashing light or motion
4) Vision or severe hearing impairment
5) Injury to eyes, face, or neck that impedes comfortable use of virtual reality
6) Diagnosed with a medical illness expected to worsen in the next 3 months (e.g., malignancy)
7) Other serious injuries that occurred with the orthopedic injury or surgical complications (e.g., infection, need for repeat surgery)
8) Current or prior untreated mental illness, substance use disorder, or suicidal ideation
9) Self-reported pregnancy
10) Currently in litigation or under Workman's Comp
11) Practice of cognitive-behavioral therapy, yoga/meditation, or other mind body techniques once per week for 45 minutes or more within the last 3 months

4b. Local Recruitment Procedures

We will recruit patients with acute orthopedic musculoskeletal injuries who are at risk for chronic pain and disability (PCS ≥ 20 and PASS-20 ≥ 40) and meet inclusionary/exclusionary criteria. With a trained RA, we will recruit patients from the MGB Orthopedics Departments through established partnerships on active trials (~220 patients/year meet criteria). Recruitment will follow a standardized protocol developed specifically for the MGH Orthopedics Department consistent with prior recommendations, [28,29] and informed by our prior IRB-approved study (protocol #: 2020P000095).[25,30] We anticipate that potential participants will be identified through daily screening of Epic admission reports by the trained RA. The RA will next notify the medical staff (medical assistant) who will alert the surgeons. The surgeon will introduce study to the potential participants at the end of the medical visit if time allows. If the surgeon does not have time to introduce the study or if additional follow up to discuss the study is needed, the RA will contact referrals via telephone to provide details and conduct a phone screen using an IRB-approved script. We will also distribute our flyer, after getting approval from site leadership, to orthopedic clinics within the larger MGB infrastructure (such as Brigham & Women's Orthopedic Trauma Department) to expand our recruitment and maximize the geographic diversity in our sample. We will not be approaching these participants in-person, but they could complete a self-reported survey for screening and will receive a call from a RA with more information. All forms of recruitment, including patient flyers, will be submitted for IRB approval prior to use.

5. Subject Enrollment

A trained RA will contact all referrals via telephone. The research assistant will make 3 attempts to contact referred potential participants before discontinuing. During the screening call, the RA will provide study details to participants and assess eligibility. The RA will be available to answer any questions from potential participants. The RA will review the consent form with eligible participants who express interest and intent to participate in the study. All participants will sign a REDCap-integrated e-consent form prior to study procedures. Individuals who do not meet study criteria or are not interested in participating will be offered a resource sheet with relevant health and mental health information for patients with acute orthopedic musculoskeletal injuries who are at risk for chronic pain and disability. The RA will maintain a detailed and updated log of all screening attempts for study data reports (i.e., % participants eligible, approached, recruited, enrolled). The principal investigator will review all cases in weekly meetings.

6. STUDY PROCEDURES

6a. Assessments

There are two assessment periods: pre-intervention (week 0) and post-intervention (week 8). Following consent, participants will complete a battery of assessments via a secure REDCap link. Participants will have the option to complete post-intervention assessments in-person or remotely. All assessments are reliable, valid, and were selected according to our prior studies in this population and (protocol #: 2020P000095) and guidelines for VR studies for pain.[12,18,19] Only trained study staff will have access to the assessment data. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept separately under lock and key. Participants will have a password-protected account for downloading the data.

The self-report assessments include:

1) Demographic factors (potential moderators): to assess age, gender, biological sex, race/ethnicity, educational level, employment status, occupation, income, marital status, mental health history, current psychotropic/pain medication intake. Pre-intervention only.
2) Clinical factors (potential moderators): to assess pain location, medical procedures and pain medications throughout study, medical comorbidities. Pre, post (chart review and self-report).
3) Credibility and Expectancy questionnaire (primary feasibility marker): to assess treatment credibility and expectancy. Pre-intervention only.
4) PROMIS Physical Function (secondary outcome): to assess one's ability to carry out activities that require physical actions, ranging from self-care to social and work. Pre, post.
5) Short Musculoskeletal Functional Assessment questionnaire (secondary outcome): to assess disability specific to musculoskeletal injury and pain. Pre, post.
6) Numerical Rating Scale (secondary outcome): to assess pain intensity. Pre, post.
7) PROMIS Sleep Disturbance Scale (secondary outcome): to assess problems with sleep and sleep quality. Pre, post.
8) Pain Catastrophizing Scale (secondary outcome) to assess catastrophic thinking about pain. Pre, post.
9) Pain Anxiety Scale (secondary outcome): to assess pain-specific anxiety. Pre, post.
10) Center for Epidemiologic Study of Depression (secondary outcome): to assess depression. Pre, post.
11) Defense and Veterans Pain Rating Scale (secondary outcome): to assess pain interference. Pre, post.
12) Pain Self-Efficacy Questionnaire (secondary outcome): to assess confidence to engage in physical activity despite pain. Pre, post.
13) Chronic Pain Acceptance Questionnaire (secondary outcome): to assess ability to engage in meaningful activities despite pain. Pre, post.
14) Cognitive and Affective Mindfulness Scale (secondary outcome): to assess state of mindfulness taught during the program. Pre, post.
15) Measure of Current Status (secondary outcome): to assess general coping ability taught during the program. Pre, post.
16) Patient's Global Impression of Change (secondary outcome): to assess perceptions of overall improvement in pain and physical function during the program. Post-intervention only

17) Client Satisfaction Questionnaire (primary feasibility marker): to assess satisfaction with treatment. Post-intervention only.
18) Motion Sickness and Nausea (primary feasibility marker): to assess adverse experiences with VR. Post-intervention only.
19) System Usability Scale (primary feasibility marker): to assess global user experience of the VR. Post-intervention only.
20) Program Feedback: to assess satisfaction with the study procedures, VR device, and study team. Post-intervention only.

After the self-reports, the trained RA will set up the non-invasive fNIRS. fNIRS monitors brain activity by recording changes in detectoxyhemoglobin, deoxyhemoglobin, and total hemoglobin concentration. It is a flexible, portable, easy to use, and sensationless imaging technique for detecting objective pain signatures in the brain. fNIRS is currently being used by other investigators on MGB IRB-approved studies (NCT05258591). Participants will be asked to sit on a chair and wear an elastic fNIRS system 10-20 cap on their head during normal extremity movements and while using the VR. The cap will have 8 mounted optodes (4 on each hemisphere) that will be located over the prefrontal cortex. The cap size will be determined by participants' circumstance of head (measurement tape will be position right above eyebrows and inion). The cap will be positioned at the proper location by the research team and, to make sure the participant is comfortable, transmitters and receivers pressure will be adjusted based on participants' feedback.

We will compensate participants $25 for completing the pre-intervention and $25 for completing the post-intervention assessments ($50 total).

6b. Intervention Period

Enrolled participants that completed the baseline assessments will progress to the intervention period. Participants will receive the *RelieveVRx* program loaded in a Pico G2 4k head-mounted VR device at no cost. The Pico G2 4K device is commercially available, widely used, inexpensive, have minimal visual latency, and are easier for participants to use than many other devices (Figures 1 and 2). Importantly, the Pico G2 4k headset only records module completion and time. It does not collect or store biometric data on participants (e.g., eye tracking, breathing).

Figure 1. Participant view of *RelieveVRx* program.

Figure 2. Pico G2 4k head-mounted VR device and controller.

The package will also include a study welcome letter from the PI, patient-friendly instructions, a charger, and a pre-paid envelope to return the VR after the intervention period. Participants will be instructed to

self-administer 1 module of at-home VR (*RelieveVrx*) daily for 8 weeks. The RA will monitor participant completion of the device use in Curebase (modules completed, time worn) and daily logs (sent by Twilio) in REDCap. Curebase is a password-protected, HIPAA- compliant, online platform used in prior studies of *RelieveVRx.*[18,19] The RA will contact participants to problem-solve barriers to VR use after 24 hours of non-wear.

The standardized 8-week VR program (*RelieveVrx*) delivers a multifaceted combination of pain relief skills training through a prescribed sequence of daily immersive experiences. The modules are informed by evidence-based principles of CBT, mindfulness, and pain neuroscience education. Each VR module is 2-16 minutes in length (average of 6 minutes). The VR treatment modules were designed to minimize triggers of emotional distress or cybersickness. Participants will complete the following *RelieveVrx* treatment modules:

- Pain education: visual and voice-guided lessons establish a medical and scientific rationale for the VR exercises and behavioral medicine skills for pain relief.
- Relaxation/Interoception: scenes that progressively change from busy/active to calm in order to train users to understand the benefits of progressive relaxation. User exhalation is measured by the microphone embedded in the Pico G2 hardware, offering biofeedback-enhanced relaxation exercises.
- Mindful escapes: high-resolution 360 videos with therapeutic voiceovers, music, guided breathing, and sound effects designed to maximize the relaxation response and participant engagement.
- Pain distraction games: interactive games to train the skill of shifting focus away from pain.

Participants will receive text messages from Twilio, an MGH-approved smartphone app that our team has successfully used in similar R34 and U01 intervention development trials, to deliver daily study reminders and biweekly pain surveys (intensity and pain interference) during the intervention period.[18,19] Participants will be informed of texting risks and provide consent for text messaging in writing or verbally if preferred. Participants will have the opportunity to ask questions about texting with study staff. Approval of text messaging and/or opting out of text messaging will be recorded in each participant's file. Participants may opt-out of the text message contact option at any point. This notification procedure was informed by prior orthopedic and pain participants in focus groups and exit interviews.[30–32]

After the 8-week intervention period, the RA will contact participants again to schedule a return visit. The RA will repeat the assessment procedures for the self-reports and the non-invasive fNIRS. After completing the post-intervention assessments, participants will be invited to participate in individual exit interviews (30 min). The PI will conduct the exit interviews with an IRB-approved semi-structured interview script. If study participants are unable to schedule a 90-minute visit, post-tests and exit interviews may be conducted virtually at an alternate time. The purpose is to gather detailed feedback on intervention components, measures, procedures, and user experience with the VR.

7. Risks and Discomforts

Patients will be informed that the foreseeable physical risks from this research study are minimal. They will be informed that there is some risk of breach of privacy/confidentiality associated with the use of text messaging, videoconferencing, and virtual reality. We specifically selected the Pico G2 4k headset because, in contrast with other commercial VR (e.g., Oculus, owned by Facebook), it does not collect

personal information on participants (e.g., demographics, biometrics, tracking/location). They will also be informed of the unlikely situation that they might feel uncomfortable with the topic of pain management and informed to contact the who will provide help, as needed. The PI is an experienced clinical psychologist who has specific expertise with orthopedic injury and pain. They will also be informed that they may feel uncomfortable completing various psychological questionnaires and that they may find it time-consuming to participate in the 8-week program.

Risk to participating in the VR program are minimal. Patients have a small risk of experiencing motion sickness or mild nausea when initially adjusting to the VR. In a recent double-blind efficacy trial that tested the *RelieveVRx* program used in this study, only 5 of 75 participants (6.7%) reported initial motion sickness.[19] All of the cases of motion sickness were mild and quickly resolved without further issues. All referring clinicians will be asked to document that there are no medical contraindications for participating in VR. For patients not referred from clinics, we will ensure that this information is collected prior to enrollment. We will comprehensively assess safety during enrollment using guidelines for VR studies of pain.[18,19] This includes: current or prior diagnosis of epilepsy, seizure disorder, dementia, migraines, or other neurological diseases; medical condition predisposing to nausea or dizziness; hypersensitivity to flashing light or motion; vision or severe hearing impairment; injury to eyes, face, or neck that impedes comfortable use of VR. We will be encouraged to contact the PI and RA as soon as possible in the unlikely event of any problems with device safety or adverse events during their treatment.

In the unlikely event that a participant is determined to be in distress or actively suicidal and at risk for self-harm during any study procedure, we will use a standardized protocol for assessing and monitoring risk developed by the PI that has been successfully used in other remote trials. In this protocol, the RA would contact the PI and the appropriate clinical intervention would be executed. In case we are unable to contact the participant we will contact their safety contacts. In case suicidality is determined during the intervention or control sessions, the PI will perform safety procedures in real time. We do not expect this unlikely event to occur, as there were no previous occurrences in our previous studies. Further, we set serious mental illness and current suicidal ideation as exclusion criteria to further reduce the chance that enrolled participants would express harm towards themselves or others during the study.

There are no risks or discomforts with the fNIRS. Participants will wear the device with an elastic cap to avoid irritation caused by skin placement. Participants may temporarily experience discomfort and/or frustration while performing normal extremity movements during the brain activation scan.

As mentioned above, we will be using secure email to communicate with participants. All email communication with participants will be encrypted using the send secure function. To further protect participants' confidentiality, we will discourage participants from communicating about medical issues by non-secure email.

8. Benefits

No direct benefit is anticipated. Participants may improve their ability to cope with pain and improve their mood, pain, and disability. Information gained through this study may lead to a better understanding the importance of delivery method of mind body interventions. The potential benefits from this study far outweigh the potential risks. The data collected as part of this study may ultimately

help researchers and clinicians develop novel digital therapeutics to better care for patients with acute injuries to prevent chronic pain and disability.

9. Statistical Analysis

We will not test for efficacy of the VR program, in line with guidelines for feasibility studies[33,34] and the NIH Stage Model[20] and NCCIH framework.[21] Instead, we will calculate frequency and proportions to assess feasibility Go/No-go benchmarks consistent with virtual pilot studies of mind-body interventions (see table below).[35–40] Power analysis is not appropriate for small feasibility pilot studies. The sample size of 10 is appropriate for early feasibility testing and achieving thematic saturation in the exit interviews. [35–40]Participants who drop-out will be counted as not meeting applicable feasibility criteria. If these benchmarks are not met, revisions will be necessary prior to an efficacy trial.[39 106] Exploratory analyses: I will calculate paired t-tests, effect sizes of improvement, and exploratory correlations for each quantitative measure.[41]

Feasibility markers	Acceptable	Excellent
Credibility and Expectancy	>70% score over scale midpoint	≥ 80% score over scale midpoint
Client Satisfaction Score	> 70% score over scale midpoint	≥ 80% score over scale midpoint
Feasibility of recruitment	> 70% approached participate	≥ 80% of approached participate
Acceptability of treatment	> 70% attend 6 out of 8 weeks	≥ 80% attend 6 out of 8 weeks
Adherence to pain survey	> 70% of biweekly surveys	≥ 80% of biweekly surveys
Feasibility of assessments	> 70% have no measures missing	≥ 80% have no measures missing
System Usability	> 70% score over scale midpoint	≥ 80% score over scale midpoint
Motion Sickness/Nausea	> 70% score below scale midpoint	≥ 80% score below scale midpoint
Other Adverse Events	Minimal	None

We will analyze qualitative data from the exit interviews using NVIVO 12 using the framework method[42,43] and a hybrid inductive-deductive approach.[44,45] This will include predetermined themes[105] while allowing for inductive flexibility where themes and codes are induced by data to allow for novel ideas to optimize the VR program.[87,103] We will code the raw qualitative data and the RA will perform reliability coding. The PI resolve discrepancies with the RA to achieve sufficient reliability (kappa > .80). We will use the qualitative feedback to improve the study procedures for subsequent trials. [46,47]

10. Monitoring and Quality Assurance

Study data will be maintained in a locked filing cabinet and on password protected computers. Questionnaires and self-reported responses will not become part of the patient's medical record and will not contain medical record numbers or names. Hardcopies of study related data and forms will be

stored in a lockable file cabinet. Patient information will remain confidential by keeping identifying information (name, medical record number, and subject number) in a separate locked file cabinet. Only the investigators and study staff specified on the consent form will have access to this information.

Adverse Event Monitoring: Throughout the study subjects will be monitored for the occurrence of events defined as any undesirable experience or unanticipated risk. Lack of effect of treatment is not considered an event. All adverse events will be reported on an adverse event form. The PI has the responsibility of reporting serious adverse events (death, life threatening illness or injury, serious injury, or permanent disability) to PHRC within 24-72 hours of notification.

A unique anonymous identifier will be assigned to each subject; subsequently, all data collected will be associated exclusively with this identifier. This includes all questionnaires administered over the course of the study, as well as pain surveys and VR use data.

Electronic information will be stored in REDCap (Research Electronic Data Capture), a free, secure, and HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing Enterprise Research Infrastructure & Services (ERIS) group (based at the PHS Needham corporate datacenter). Data will be stored on password protected computers that will be always stored in secure locations. Paper data files (with coded subject identification) will be stored in a locked filing cabinet. Only research staff will have access to these data locations.

The VR program, RelieveVRx, will transmit data when participants wear the Pico headset (treatment modules completed, time worn) via Curebase. Curebase is a password-protected, HIPAA- compliant, online platform. Curebase is used by the developer of the RelieveVRx, Applied VR, for clinical trials. Virtual reality use data transmitted by Curebase will be encrypted with a unique identifier and stored in a secure encrypted cloud-based software (AWS) and a password-protected Excel database. The database will have a participant number and no personal identifiers associated with the virtual reality use data.

The exit interviews will be audio recorded for transcription and qualitative analysis. The audio recordings will be stored on a password protected drive and deleted once transcribed. The transcriptions will be de-identified.

Data from this study will be stored for three years after the publication of all study results, at which time all paper data files will be shredded, and computer files will be deleted.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol

- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☒ Additional privacy and/or confidentiality protections: We specifically selected the Pico G2 4k headset because, in contrast with other commercial VR (e.g., Occulus, owned by Facebook), it does not collect personally information on participants (e.g., demographics, biometrics, tracking/location).

12. References

1. Morris S, Lenihan B, Duddy L, O'Sullivan M. Outcome after musculoskeletal trauma treated in a regional hospital. *J Trauma*. 2000;49(3):461-469. doi:10.1097/00005373-200009000-00013

2. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth*. 2019;123(2):e273-e283. doi:10.1016/j.bja.2019.03.023

3. Musculoskeletal conditions. Accessed April 27, 2022. https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions

4. Proctor TJ, Mayer TG, Gatchel RJ, McGeary DD. Unremitting health-care-utilization outcomes of tertiary rehabilitation of patients with chronic musculoskeletal disorders. *J Bone Joint Surg Am*. 2004;86(1):62-69. doi:10.2106/00004623-200401000-00011

5. Vranceanu AM, Bachoura A, Weening A, Vrahas M, Smith RM, Ring D. Psychological factors predict disability and pain intensity after skeletal trauma. *J Bone Joint Surg Am*. 2014;96(3):e20. doi:10.2106/JBJS.L.00479

6. Turner JA, Anderson ML, Balderson BH, Cook AJ, Sherman KJ, Cherkin DC. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. *Pain*. 2016;157(11):2434-2444. doi:10.1097/j.pain.0000000000000635

7. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA*. 2016;315(12):1240-1249. doi:10.1001/jama.2016.2323

8. Westenberg RF, Zale EL, Heinhuis TJ, et al. Does a Brief Mindfulness Exercise Improve Outcomes in Upper Extremity Patients? A Randomized Controlled Trial. *Clin Orthop Relat Res*. 2018;476(4):790-798. doi:10.1007/s11999.0000000000000086

9. Chad-Friedman E, Talaei-Khoei M, Ring D, Vranceanu AM. First Use of a Brief 60-second Mindfulness Exercise in an Orthopedic Surgical Practice; Results from a Pilot Study. *Arch Bone Jt Surg*. 2017;5(6):400-405.

10. Crombez G, Eccleston C, Van Damme S, Vlaeyen JWS, Karoly P. Fear-avoidance model of chronic pain: the next generation. *Clin J Pain*. 2012;28(6):475-483. doi:10.1097/AJP.0b013e3182385392

11. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85(3):317-332. doi:10.1016/S0304-3959(99)00242-0

12. Darnall BD, Scheman J, Davin S, et al. Pain Psychology: A Global Needs Assessment and National Call to Action. *Pain Med*. 2016;17(2):250-263. doi:10.1093/pm/pnv095

13. Vranceanu AM, Beks RB, Guitton TG, Janssen SJ, Ring D. How do Orthopaedic Surgeons Address Psychological Aspects of Illness? *Arch Bone Jt Surg*. 2017;5(1):2-9.

14. Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf*. 2018;27(5):526-534. doi:10.1002/pds.4278

15. Mallari B, Spaeth EK, Goh H, Boyd BS. Virtual reality as an analgesic for acute and chronic pain in adults: a systematic review and meta-analysis. *J Pain Res*. 2019;12:2053-2085. doi:10.2147/JPR.S200498

16. Colloca L, Raghuraman N, Wang Y, et al. Virtual reality: physiological and behavioral mechanisms to increase individual pain tolerance limits. *Pain*. 2020;161(9):2010-2021. doi:10.1097/j.pain.0000000000001900

17. Keefe FJ, Huling DA, Coggins MJ, et al. Virtual reality for persistent pain: a new direction for behavioral pain management. *Pain*. 2012;153(11):2163-2166. doi:10.1016/j.pain.2012.05.030

18. Darnall BD, Krishnamurthy P, Tsuei J, Minor JD. Self-Administered Skills-Based Virtual Reality Intervention for Chronic Pain: Randomized Controlled Pilot Study. *JMIR Formative Research*. 2020;4(7):e17293. doi:10.2196/17293

19. Garcia LM, Birckhead BJ, Krishnamurthy P, et al. An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: Double-Blind, Randomized, Placebo-Controlled Trial Conducted During COVID-19. *J Med Internet Res*. 2021;23(2):e26292. doi:10.2196/26292

20. Onken LS, Carroll KM, Shoham V, Cuthbert BN, Riddle M. Reenvisioning Clinical Science: Unifying the Discipline to Improve the Public Health. *Clin Psychol Sci*. 2014;2(1):22-34. doi:10.1177/2167702613497932

21. National Center for Complementary and Integrative Health (NCCIH. Framework for Developing and Testing Mind and Body Interventions. Grants and Funding. Published 2020. Accessed September 1,

2020. https://www.nccih.nih.gov/grants/framework-for-developing-and-testing-mind-and-body-interventions

22. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res*. 2011;45(5):626-629. doi:10.1016/j.jpsychires.2010.10.008

23. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10(2):307-312. doi:10.1111/j..2002.384.doc.x

24. "Rules" of evidence in assessing the efficacy and effectiveness of treatments - PubMed. Accessed April 28, 2022. https://pubmed.ncbi.nlm.nih.gov/14561567/

25. Vranceanu AM, Jacobs C, Lin A, et al. Results of a feasibility randomized controlled trial (RCT) of the Toolkit for Optimal Recovery (TOR): a live video program to prevent chronic pain in at-risk adults with orthopedic injuries. *Pilot Feasibility Stud*. 2019;5:30. doi:10.1186/s40814-019-0416-7

26. Jacobs CA, Mace RA, Greenberg J, et al. Development of a mind body program for obese knee osteoarthritis patients with comorbid depression. *Contemp Clin Trials Commun*. 2021;21:100720. doi:10.1016/j.conctc.2021.100720

27. Gewandter JS, Dworkin RH, Turk DC, et al. Improving study conduct and data quality in clinical trials of chronic pain treatments: IMMPACT recommendations. *J Pain*. 2020;21(9-10):931-942. doi:10.1016/j.jpain.2019.12.003

28. Proctor E, Silmere H, Raghavan R, et al. Outcomes for Implementation Research: Conceptual Distinctions, Measurement Challenges, and Research Agenda. *Adm Policy Ment Health*. 2011;38(2):65-76. doi:10.1007/s10488-010-0319-7

29. Powell BJ, Waltz TJ, Chinman MJ, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implementation Science*. 2015;10.

30. Bakhshaie J, Doorley J, Reichman M, et al. Optimizing the implementation of a multisite feasibility trial of a mind-body program in acute orthopedic trauma. *Transl Behav Med*. Published online February 23, 2022:ibac004. doi:10.1093/tbm/ibac004

31. Doorley JD, Mace RA, Popok PJ, Grunberg VA, Ragnhildstveit A, Vranceanu A. Feasibility Randomized Controlled Trial of a Mind-Body Activity Program for Older Adults with Chronic Pain and Cognitive Decline: The Virtual "Active Brains" Study. *The Gerontologist*.

32. Mace RA, Doorley JD, Popok PJ, Vranceanu AM. Live video adaptations to a mind-body activity program for chronic pain and cognitive decline: Protocol for the "Virtual Active Brains" study. *JMIR Res Protoc*. Published online November 13, 2020. doi:10.2196/25351

33. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research*. 2011;45(5):626-629. doi:10.1016/j.jpsychires.2010.10.008

34. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *Journal of Evaluation in Clinical Practice*. 2004;10(2):307-312. doi:10.1111/j.2002.384.doc.x

35. Lester EG, Hopkins SW, Popok PJ, Vranceanu AM. Adaptation of a Live Video Mind-Body Program to a Web-Based Platform for English-Speaking Adults With Neurofibromatosis: Protocol for the NF-Web Study. *JMIR Res Protoc*. 2021;10(6):e27526. doi:10.2196/27526

36. Greenberg J, Lin A, Zale EL, et al. Development and early feasibility testing of a mind-body physical activity program for patients with heterogeneous chronic pain; the getactive study. *Journal of Pain Research*. 2019;12:3279-3297. doi:10.2147/JPR.S222448

37. Jacobs CA, Mace RA, Greenberg J, et al. Development of a mind body program for obese knee osteoarthritis patients with comorbid depression. *Contemporary Clinical Trials Communications*. 2021;21(January):100720. doi:10.1016/j.conctc.2021.100720

38. Lester E, DiStefano S, Mace R, Macklin E, Plotkin S, Vranceanu AM. Virtual mind-body treatment for geographically diverse youth with neurofibromatosis: A pilot randomized controlled trial. *Gen Hosp Psychiatry*. 2020;62:72-78. doi:10.1016/j.genhosppsych.2019.12.001

39. Mace R, Greenberg J, Stauder M, Reynolds G, Vranceanu A. My Healthy Brain: A multimodal lifestyle program to promote brain health. *Aging Ment Health*. Published online 2021.

40. Mace RA, Doorley JD, Popok PJ, Vranceanu AM. Live Video Adaptations to a Mind-Body Activity Program for Chronic Pain and Cognitive Decline: Protocol for the Virtual Active Brains Study. *JMIR Res Protoc*. 2021;10(1):e25351. doi:10.2196/25351

41. National Institutes of Health. Science of behavioral change. Published 2021. https://commonfund.nih.gov/behaviorchange

42. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*. 2013;13(1). doi:10.1186/1471-2288-13-117

43. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: *Analyzing Qualitative Data*. ; 2010:173-194. doi:10.4324/9780203413081_chapter_9

44. Mace RA, Gates M V, Bullard B, et al. Development of a Novel Mind–Body Activity and Pain Management Program for Older Adults With Cognitive Decline. *The Gerontologist*. Published online 2020. doi:10.1093/geront/gnaa084

45. Greenberg J, Singh T, Iverson GL, et al. A Live Video Mind-Body Treatment to Prevent Persistent Symptoms Following Mild Traumatic Brain Injury: Protocol for a Mixed Methods Study. *JMIR Research Protocols*. 2021;10(1):e25746. doi:10.2196/25746

46. National Institutes of Health. NIH Stage Model for Behavioral Intervention Development. https://www.nia.nih.gov/research/dbsr/nih-stage-model-behavioral-intervention-development

47. Onken LS, Carroll KM, Shoham V, Cuthbert BN, Riddle M. Reenvisioning Clinical Science: Unifying the Discipline to Improve the Public Health. *Clinical Psychological Science*. 2013;2(1):22-34. doi:10.1177/2167702613497932

APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☐ The DMC/DSMB is independent from the study team and study sponsor.

☐ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☐ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☐ Describe number and types of (i.e., qualifications of) members:
Click or tap here to enter text.

☐ Describe planned frequency of meetings:
Click or tap here to enter text.

☐ DMC/DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☐ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.