Pain Rehabilitation Virtual Reality (PRVR)
Innovations to Enhance Mobility in the Presence of Pain @ HOME

Pediatric Pain Rehabilitation with Virtual Reality (PR-VR) Feasibility Study

Clinical Protocol

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Affected Section(s)	Summary of Revisions Made	Rationale

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Clinical Research Coordinator	Department of Anesthesiology, Perioperative and Pain Medicine Stanford University School of Medicine [redacted] Palo Alto, CA 94304	[redacted]	[redacted]	Study Coordinator -Participant identification, screening, enrollment, and retention -Data entry and management

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Study Abbreviations

Acronym	Expanded Term
AE	Adverse Event
ANOVA	Analysis of Variance
BAS	Baseline study visit
CITI	Collaborative Institutional Training Initiative
CRC	Research Coordinator
DSMP	Data Safety Monitoring Plan
eCRF	Electronic Case Report Form
END	Discharge
FDA	Food and Drug Administration
FU	Follow Up
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MCID	Minimally Clinical Important Difference
MSK	Musculoskeletal Pain
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSF	Online Screening Form
PD	Protocol Deviation
PI	Principal Investigator
PID	Participant Identification Number
PRVR	Pain Rehabilitation Virtual Reality
PT	Physical Therapy/Therapist
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SCH	Stanford Children's Health
SMC	Safety Monitoring Committee
SR	Self-Report
UP	Unanticipated Problem

PARTICIPATING STUDY SITES

The study will be conducted at the Department of Rehabilitation at Stanford Children's Health (SCH) at the Pediatric Pain Management Clinic (PPMC).

PRÉCIS

Study Title

Pain Rehabilitation Virtual Reality (PRVR) Innovations to Enhance Mobility in the Presence of Pain // Pediatric Pain Rehabilitation with Virtual Reality (PRVR) Feasibility Study

Objectives

For many adolescents suffering with chronic pain, fear associated with movement and return to activities significantly interferes with clinical improvement. Prior research supports virtual reality (VR)'s ability to reduce fear of movement-related pain, provide distraction from pain symptoms, encourage increased range of motion, improve endurance, facilitate postural improvements, and enhance tolerance to sensory stimuli for desensitization. Thus, VR has vast potential to become an instrumental tool in pediatric pain rehabilitation programs.

We conducted a pilot study of the pain rehabilitation virtual reality (PRVR) platform, which included the development and feasibility testing of a number of unique VR experiences for youth undergoing chronic pain treatment and rehabilitation. With iterated improvement based on patient feedback, these VR rehabilitation experiences feature mirror therapy, exaggerated movement capabilities, biofeedback, and a Clinical Research Tool that tracks movement of each extremity in real-time with advanced analytic capabilities. Results from patients and clinicians (psychology, physical therapy, occupational therapy) in this study supported the PRVR platform as an acceptable, feasible, and useful intervention in this patient setting.

Design and Outcomes

This is a single arm feasibility study. **A "participant" in this study is defined as a child and at least one parent**. The **primary outcomes are** feasibility, acceptability, and utility of VR. The **secondary outcomes** are physical function (child only) and pain-related fear and avoidance (child).

Interventions and Duration

All participants will receive an Oculus Quest 2 virtual reality (VR) headset for use during their treatment at the PPMC. VR will supplement treatment and be used in session (either in-person or telehealth) and at home as part of their prescribed treatment homework.

Sample Size and Population

Patients who meet eligibility criteria will be referred to the study by their clinician at clinic appointments.

2. BACKGROUND AND RATIONALE

2.1 Background and Significance

Overall Scientific Premise. Chronic musculoskeletal (MSK) pain in adolescence is a significant public health concern with median prevalence rates of 11 to 38%[1,2], with 3 to 5% of adolescents suffering from significant pain-related disability[25,26], costing society $19.5 billion annually in the US alone[3]. Notwithstanding the personal suffering and persistent physical and economic consequences for families, chronic pain in adolescence can predispose the development of adult chronic pain[27]. Progressively increasing activity in the presence of pain is critical for effective functional restoration in chronic MSK pain in adolescents[6] and adults[7-13] with physiotherapy (PT) a critical ingredient[14]. Despite the widespread use of Standard Physiotherapy Rehabilitation (SPR)[15], daring to increase movement while in pain can often feel physically and emotionally unattainable with fear of pain a particularly salient influence on pain outcomes[16-19],

hindering clinical improvement[20]. Virtual reality (VR) has the potential to break the vicious cycle of fear of movement and avoidance during PT. VR provides access to a multisensory, three-dimensional (3D) immersive experience to overcome obstacles that seem insurmountable in the real world. Thus, the current study tests pain rehabilitation virtual reality (PRVR) for adolescents with chronic MSK pain. PRVR was created with input from a multidisciplinary collaborative team of pediatric rehabilitation providers and patient end users, alongside VR technology developers in response to the growing need for VR programming specific to pediatric chronic pain populations whose mobility has been limited due to pain, fear and activity avoidance. PRVR gamifies PT, helping patients increase their range of motion and become more comfortable moving their bodies to achieve game objectives. The games offer a combination of acute distraction from pain, reinforcement of movement, and progressive increases in range of motion. With evidence that VR holds promise for chronic pain rehabilitation in adults[23,24,28] and compelling preliminary results from our feasibility-tested immersive PRVR intervention, this feasibility study will provide the necessary findings to support or refute the feasibility of scale implementation of PRVR, a tailored treatment option for adolescents struggling with persistent MSK pain, fear, and disability.

Scientific premise for Virtual Reality. The application of VR in healthcare has rapidly accelerated in recent years due to increased market availability and declining costs. VR enables the user to interact with a computer-generated environment that harnesses sensory inputs (e.g., visual, audio, tactile) to provide an immersive experience to facilitate reaching therapeutic goals. Most commonly applied in the context of acute pain relief, research is emerging for its application in the realm of chronic pain rehabilitation. VR has been suggested as an alternative to opioids with the therapeutic mechanisms centered on distraction[29,30], neuromodulation of body perception[31], and graded exposure to feared/avoided movements[23,24,28,32]. Moreover, VR can potentially enhance motivation and engagement during physical rehabilitation, facilitate repetitive motions, and incorporate real-time and longitudinal feedback for the patient and clinician[33-36]. Perhaps most exciting is the prospect of VR to engage several cortical and subcortical neuronal circuits that potentiate learning and recovery[37,38] with the potential for enhanced cortical reorganization[39,40]. The extant literature includes proof of concept, feasibility, and pilot RCT studies. One recently published study of VR combined with exercise for adults with fibromyalgia demonstrated greater improvements in pain, fear of movement, fatigue, level of physical activity, and quality of life when compared to exercise alone[28]. Overall, many studies report promising outcomes yet lack the rigor and measurement over time critical to establish VR as an evidence-based treatment for chronic pain rehabilitation.

Scientific premise for physical activity monitoring. A cycle of fear of movement and activity avoidance in adolescents with chronic pain can lead to decreased tolerance of physical activity that persists into adulthood[41]. Abnormal kinesics, such as asymmetry in range of motion, or timing of muscle activation or joint motions, commonly exist as a compensatory mechanism in chronic pain[41-43], potentially amplified by pain-related fear[44]. This trial will include self-report, objective tests of physical function[45,46] coupled with real world objective physical activity monitoring via a wrist-worn actigraph. Actigraphy is particularly useful as self-report measures can be prone to response shift and reporter bias[47,48]. Unlike laboratory-based objective measures of physical activity, such as timed walks and peak oxygen consumption during exercise, actigraphy provides high ecological validity with unobtrusive measurement of activity levels during daily life[49] with adolescents with chronic pain having lower mean and peak activity levels compared to healthy peers[48].

Significance of the expected research contribution: (1) harnessing immersive technology to overcome fear of movement in the presence of pain, (2) providing real-time feedback in a gamified context to sustain motivation and adherence, and (3) purposefully capturing both objective (physical function assessment, actigraphy) and subjective (self-report) daily functioning to define clinical endpoints and assess treatment progress in the clinic and at home.

Innovation

Treatment of chronic pain remains a tremendous challenge[51]. Developing mechanistically informed and innovative treatment approaches results in optimal clinical care. This application shifts current research and clinical practice by: **(1) Increasing physical functioning using a motivating and gamified context with concomitant decreases in fear of pain.** PRVR targets functional improvement through harnessing the immersive and fun elements of VR gaming. Making gains in physical function and movement is not only highly reinforcing in itself, we have shown that it can lead to changes at the neural circuit level in somatosensory and motor processing while simultaneously decreasing fear of pain[52]. **(2) Leveraging digital solutions.** Emerging trends in healthcare call for a precision medicine approach[53] with its success contingent on the collection of patient data across domains as well as the development of efficient and effective targeted treatments. Digital health has the potential to integrally contribute to both data collection and intervention and is at the core of the current proposal. Data collected from the child (electronic daily diary, actigraphy, wearable sensors in VR) can be communicated to providers to inform clinical decision-making and support tailored, point of care decisions that result in science-forward, targeted, and effective interventions. We envision this synergistic and dynamic model (**Figure 1;** Richardson et al., *in submission*) as the future of evidence-based treatment for pediatric chronic pain. **(3) Nonpharmacological solution with the potential for brain circuit engagement.** Identifying nonpharmacological interventions for adolescents is critical as few analgesics or psychotropics have documented long-term safety and efficacy in the developing brain and opioids are known to have adverse long-term effects on the brain[54]. Given we have demonstrated neural plasticity of adolescents with chronic pain after pain rehabilitation[52,55,56] and the prospect of VR to engage cortical and subcortical neuronal circuits that potentiate learning and recovery[37,38] and the potential for enhanced cortical reorganization[39,40], testing the effectiveness of VR for adolescents with MSK pain is justified. *Overall, the momentum is building in the field of VR for pain with over 100 active studies registered at ClinicalTrials.gov with this study representing the first targeting adolescents with MSK pain, thus, this proposal is timely.*

Figure 1. Transforming Healthcare with Digital Solutions

2.2 Study Rationale

Preliminary Studies/Progress Report

Preliminary Data to Support Aim 1.

(a) Human-centered design and feasibility testing of PRVR. The pediatric pain rehabilitation team at Stanford Children's Health (SCH) worked collaboratively with the Stanford CHARIOT Program and consultant **Luke Wilson** (Mighty Immersion, Inc.) to develop PRVR content, *Fruity Feet* (Griffin et al., *in submission*). *Fruity Feet* was developed using a human-centered approach with patient and clinician end-user feedback across four phases: (1) Needs Assessment, (2) Prototyping, (3) Iteration and Refinement, and (4) Feasibility and Acceptability. It was designed to be developmentally appropriate for youth by focusing on fun, while leaning on stylized graphics and encouraging in-game feedback. Gameplay mechanics were built around PT movement goals, for example for lower extremity: multiplanar stepping (i.e., forward, side, back), stomping, marching, kicking, raising leg to different heights, and active ankle range of motion tasks. Importantly, it was also built to scale to a patient's mobility, ensuring that patients

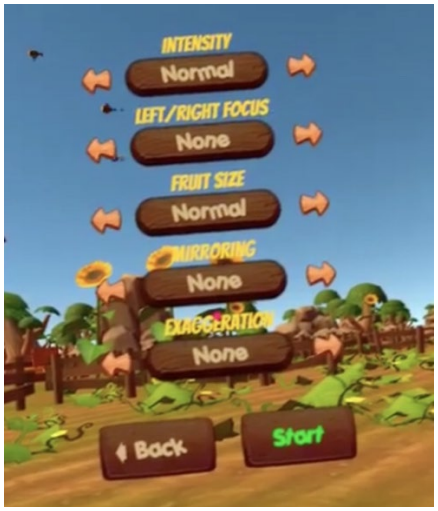
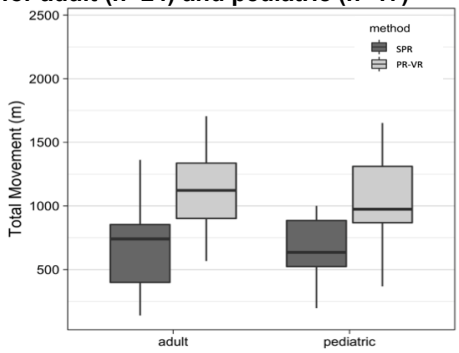


Figure 4. Fruity Feet settings. Providers can adjust the game to fit patient needs. *Intensity* affects rate fruit appears. *Left/Right Focus* encourages use of affected side. *Fruit Size* affects foot lift to stomp fruit. *Extremity Focus* focuses on lower or upper extremities. *Foot/Hand Mirroring* mirrors the virtual extremity, like mirror-therapy. *Foot/Hand Exaggeration* amplifies or decreases translation of real-world movement.

of all abilities could play the game and benefit from the VR intervention (**Figure 4**). *Consistent with the recommendations for VR clinical trial methodology[80], this human-centered iterative design process yielded a program that, in addition to gamification, provides backend mechanics giving PT providers the capability to control intensity, affected side/extremity emphasis, mirroring, and movement exaggeration to leverage the potential neuromodulatory effects of VR coupled with targeted pain PT.*

(b) PRVR increases movement. A prospective, randomized crossover study led by Co-Investigator **Tom Caruso, MD** compared PRVR vs. SPR ages 6 and older, including adolescents (n=41) during a single session of outpatient PT with each patient serving at their own control (NCT03874507). Patients moved significantly more when participating in PRVR compared to SPR (1120.88 meters vs 672.65 meters p = 5.47E-08; **Figure 5**). When stratified by therapy target (upper vs lower) PRVR treatment was also associated with more movement of the appropriate limbs, lower (p < 0.001) and upper (p = 0.01). Pediatric users reported significantly less pain when using VR (88%) compared to adults (50%) and virtually all patients reported enjoying the VR experience (96% adult users; 100% pediatric users). (Caruso et al., *in preparation*). *These results suggest marked increases in movement, potential pain relief, and a fun experience using VR in PT and warrents examination for culmultative effects over mulitple treatment sessions.*

Figure 5. SPR vs PRVR total movement for adult (n=24) and pediatric (n=17)



Feasibility and Acceptability Data. PRVR feasibility testing (**Mayday Fund supported**) included 17 participants (13 female, 4 male), mean age 13.24 (range 7-17), completing a total of 63 sessions. Overall reports of immersion were high (M = 28.98, SD = 4.02 out of 40). Analysis of 45 sessions from 13 patients entered into the NVivo qualitative data analysis program revealed: 1) positive experience (i.e., enjoyed it, would like to utilize the VR program again, felt it was a helpful tool), 2) feeling distracted from pain while engaged in VR, 3) increased physical function/mobility, and 4) reduced pain behaviors/symptoms during VR (Griffin et al., *in submission*). *These results suggest that Fruity Feet has the right mix of immersion, fun and PT movement capabilities to provide targeted and effective pain physiotherapy in VR.*

3. STUDY DESIGN

Recruitment. Potential participants were identified at their multidisciplinary evaluation at the Pediatric Pain Management Clinic and at participating private practices. Participants will be referred by their clinician and if interested will be put in contact with Dr. Simons, her co-investigators, or trained members of the research team.

Trained members of the research team may need to contact youth and caregivers to confirm eligibility after referral. Additionally, a study flyer will be posted on a bulletin board of all active clinical studies in patient waiting rooms and/or given to eligible participants if they would like.

For inclusion, the patients: 1) are 10-17 years old; 2) have musculoskeletal or neuropathic pain (e.g., localized [back, limb], diffuse)[47] not due to an acute trauma (active sprain or fracture); 3) English language proficiency. ***Patient exclusion criteria are:*** 1) significant cognitive impairment (e.g., brain injury) and 2) significant medical or psychiatric problem that would interfere with treatment (e.g., seizures, psychosis, suicidality). 3) Presents with a condition that interferes with virtual reality usage (e.g., history of seizure, facial injury precluding safe placement of headset, visual impairment, significant hearing impairment impact ability to follow audio instructions). **Identification of Eligibility:** Patients and their parents who meet eligibility criteria will be referred to the study by their pain clinicians at clinic appointments. A trained member of the research team will reach out to the family after they are referred and they agree.

Study Procedures. After the informed assent/consent, baseline will begin, and participants will complete baseline questionnaires. Discharge testing occurs at the end of 6-8 sessions or when the clinician believes they are finished with treatment. Discharge includes participant questionnaires. At 3 months follow-up,

participants complete self-report questionnaires. VR will supplement treatment and be used in session (either in-person or telehealth) and at home as part of their prescribed treatment homework. We will ask youth and caregivers to join a training session via zoom or in person so that trained members of the research team may orientate the family to the VR equipment and help them set it up in the environment in which they will be asked to use the VR by their clinician.

Optional study procedures.

Daily Diary Surveys: Answering questions in the daily diary will take approximately 3 minutes to complete. You will be asked to fill out the daily diary and given the option to answer weekly, daily, and/or when you have PT sessions during study treatment and for one week at 3-month follow-up if you choose. You will be compensated a $20 bonus as a thank you for your time if you choose to answer these surveys.

Brief Informational Interview: This exploratory study seeks to gather reports from participants after undergoing virtual reality exposure, paying particular attention to the language individuals use to describe their experience. Thus, the study procedure may include an informal and semi-structured interview, that will take place in the clinic after VR exposure. Participants and their parents may be asked to reflect on their condition, and on their experience with the VR module. The interviews may be recorded and transcribed. Personally-identifying information will not be disclosed from these interviews. Audio devices will be kept in a locked office at Stanford University.

Actigraph Watch: Participants can wear a small, electronic study device on your wrist that tracks your activity level and sleep. If they choose to participate in this activity, participants will be asked to wear this from the start of the study until the last study treatment session and responsible for returning this electronic study device at the end of the study treatment period.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Participants will complete their treatment sessions 1-hour each, delivered over ~6-12 weeks or until clinician believes the patient is done with treatment. VR will supplement treatment and be used in session (either in-person or telehealth) and at home as part of their prescribed treatment homework.

5.1.2 Compensation

All patients will be closely monitored by the PI, Laura Simons, as well as the treatment and research team. Patients are compensated for their time and contribution to this study, with increased compensation for the 3 -month post-discharge follow-up. The following is the compensation timeline for all patients in the study:

- **Timepoint 1:** $10.00 Amazon.com gift code at the start of treatment after baseline completion of questionnaires
    - $20 bonus if participants agree to participate in the daily surveys
- **Timepoint 2:** $20.00 Amazon.com gift code after completion of treatment and end of treatment questionnaires
- **Timepoint 3:** $30.00 Amazon.com gift code at the 3 month post-discharge follow-up for completion of questionnaires

5.2 Handling of Study Interventions

All participants will receive an Oculus Quest 2 virtual reality headset for use during the study.

5.4 Adherence Assessment

Patients will be closely monitored by the PI, Laura Simons, as well as the treatment and research team. Patients are compensated for their time and contribution to this study, with increased compensation for the 3-month follow-ups. Follow-up will occur at 3-months for both treatment groups.

6. Description of Evaluations

The Schedule of Evaluations will include Recruitment (referral), a Baseline Assessment (informed consent/assent, self-reported questionnaires), Discharge Assessment (self-report questionnaires), and a 3-month follow-up (self-report questionnaires).

6.1 Screening Evaluation

Screening

The study team will recruit adolescent patients and a primary parent from the outpatient rehabilitation department the Department of Rehabilitation at Stanford Children's Health (SCH) at the Pediatric Pain Management Clinic (PPMC). Youth patient and parent will be reffered by their clinician at the PPMC. If interested, the parent will tell their clinician that they are interested to allow researchers to contact them.

Consenting Procedure

Before obtaining formal written assent/consent from patients and their parents, clinical providers at the SCH will obtain consent to be approached by members of the research team.

Study staff, which will include a clinical research coordinator (CRC) or postdoctoral fellow trained by Dr. Laura Simons, will conduct the consent and assent procedure. Eligible participants will be educated about study procedures or any changes in those procedures. Signed consent/assent forms will be kept in a locked secure database in IRB approved REDCap.

6.2 Enrollment, Baseline, and Randomization

Enrollment

Study consenting/assenting and enrollment will take place via Zoom or in person. All procedures will be completed by a clinical research coordinator (CRC) and/or postdoctoral fellows.

Consenting Procedure for Enrollment

This study will follow the *Informed Consent Process for Research* according to the Stanford University Research Compliance Office. Each participant's consenting process will be recorded by the study CRC in the "Screening and Enrollment Log" (MOP Supplemental Materials I) within an online REDCap eCRF. The signed consent/assent documents will be kept in a locked secure database in IRB approved REDCap.

The informed consent process will take place via Zoom or in-person, and participants will have the opportunity to read the consent form and ask any questions they may have at the beginning of the data collection session. Signed consent/assent forms will be stored in a locked secure database. Participants will be reminded that their involvement in this study is completely voluntary, and that they can withdraw it any time without any negative repercussions whatsoever (e.g., with regard to clinical care or healthcare access). They will also be explicitly told that they may leave any question blank for questionnaires or unanswered for the clinical interview if they do not feel comfortable answering. See Supplement Material for the consent and assent form.

Non-English Speaking Participants – Individuals who do not speak or understand English will not be recruited to the study. While we recognize the limitations of this approach, practical considerations necessitate the inclusion of only those who are able to speak or understand English.

Enrollment date will be recorded in the "Screening and Enrollment Log" eCRF, which will also include documentation of inclusion/exclusion criteria.

Baseline Assessment (BAS):

The BAS assessment will consist of self-report measures and a zoom or in-person training session. The child and parent baseline measures will be introduced by a CRC after they conduct the consent/assent process via Zoom or in person.

VR orientation: We will ask youth and caregivers to join a brief zoom call so that trained members of the research team may orientate the family to the VR equipment and help them set it up in the environment in which they will be asked to use the VR by their clinician.

See Supplemental Materials III for baseline self-report measures

Discharge Assessment:

The child and parent will complete discharge measures.

See Supplemental Materials III for discharge assessment measures

Follow-Up Assessments:

The child and parent will complete follow-up measures.

See Supplemental Materials III for follow-up assessment measures

Optional Assessments:

Daily Diary Surveys: Answering questions in the daily diary will take approximately 3 minutes to complete. You will be asked to fill out the daily diary and given the option to answer weekly, daily, and/or when you have PT sessions during study treatment and for one week at 3-month follow-up if you choose. You will be compensated a $20 bonus as a thank you for your time if you choose to answer these surveys.

Brief Informational Interview: This exploratory study seeks to gather reports from participants after undergoing virtual reality exposure, paying particular attention to the language individuals use to describe their experience. Thus, the study procedure may include an informal and semi-structured interview, that will take place in the clinic after VR exposure. Participants and their parents may be asked to reflect on their condition, and on their experience with the VR module. The interviews may be recorded and transcribed. Personally-identifying information will not be disclosed from these interviews. Audio devices will be kept in a locked office at Stanford University.

Actigraph Watch: Participants can wear a small, electronic study device on your wrist that tracks your activity level and sleep. If they choose to participate in this activity, participants will be asked to wear this from the start of the study until the last study treatment session and responsible for returning this electronic study device at the end of the study treatment period.

See Supplemental Materials III for optional assessment measures

Clinician Measures:

Clinicians will answer brief surveys post VR exposure in session to document use of VR to ensure safety of participants.

See Supplemental Materials III for clinician measures

7. SAFETY ASSESSMENTS

As the study is being conducted within a healthcare facility all normal monitoring of safety will be in place. There are few additional safety risks introduced as part of the involvement in the study

procedures. If any risk arises as part of completing study assessments or participating in the treatment, there are physical therapists and medical personnel immediately available to assess the situation and provide assistance. See Appendix B and Appendix C for Adverse and Serious Adverse Event Reporting forms.

7.1 Specification of Safety Parameters

N/A

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

N/A

7.3 Adverse Events and Serious Adverse Events

For the purposes of this study, the following AE definitions are used:

Adverse Event (AE): Any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated treatment interventions, regardless of whether it is considered related to the treatment. AEs are categorized according to the following scale:

Severity Ratings
Adverse Events (AEs) will be rated on the following three-point scale, to the determine the severity of

- ***Mild***: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.
- ***Moderate***: An experience that is alleviated with simple therapeutic treatments. This experience impacts usual daily activities. Includes laboratory tests alterations indicating injury, but without long-term risk.
- ***Severe***: An experience that requires therapeutic intervention unrelated to clinical trial treatment intervention. The experience interrupts usual daily activities. If hospitalization is required for treatment, this will be classified as an SAE.

Relatedness Ratings
Adverse Events (AEs) will be rated on the following three-point scale, to the degree to which the event appears to be related to the study intervention:

- 0, ***Unrelated***
- 1, ***Possibly Related***
- 2, ***Definitely Related***

Expectedness Ratings
Adverse Events (AEs) will be assessed as to wither they were *expected* to occur or *unexpected*, meaning not anticipated based on current knowledge found in the protocol or based on the treating clinician's experience:

- ***Unexpected***: the nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, or clinician's experience
- ***Expected***: the event is known to be associated with the intervention or condition under study.

Unanticipated Problem (UP): an unanticipated problem involving risk to human participants or others, is one that (1) was unforeseen at the time of its occurrence, (2) is related or possibly related

to participation in the research, and (3) indicates that participants or others are at an increased risk of harm.

Serious Adverse Events (SAE*)*: Any AE that result in any of the following outcomes:

- Death
- Suicide/Homicide Attempt
- Life-Threating event
- Event requiring inpatient hospitalization
- Persistent or significant escalation of disability/incapacity

There is no evidence that participation in this treatment trial will increase risk of a serious adverse event (SAE).

7.4 Reporting Procedures

AEs will be identified at any time during participation in this treatment study. Reports of AEs to the Get Living Study team will be assessed and noted. The study team will be informed to notify the PI of any AEs identified during treatment or throughout the duration of enrollment in the study. Parents of patients will also be asked to notify the study team if an AE has occurred. During follow-up contact, the study staff will ask patient and parent if any AEs have occurred since the end of treatment. The known potential risks will be described in informed consent documents and protocol.

All AEs and SAEs will be monitored on a continual basis and documented, by participant, in the respective eCRFS on REDCap. All AEs and SAEs will also be collated across participants into a Master Sheet for presentation to the Safety Monitoring Committee (SMC) at quarterly meetings. In addition, all SAEs and UPs are reported according to the Stanford Medical IRB reporting guidelines (within 10 working days of occurrence). Follow-up remediation will occur within five days of the IRB's response or decision. All AEs will be reviewed quarterly by the PI and SMC.

SAEs and specific treatment intervention-associated AEs will be reported to the PI, Dr. Laura Simons, and responsible study staff within 24 hours. All SAEs and UPs will be reported to the NIAMS within 48 hours of the investigator becoming aware of the event. There are no SAEs anticipated for this research study.

7.5 Follow-up for Adverse Events

All AE's will be reported to the IRB of record within five days. Follow-up remediation will occur within five days of the IRB's response or decision.

7.6 Safety Monitoring

Oversight of this clinical trial is provided by the Principal Investigator (PI), Dr. Simons. The Study Monitoring Committee (SMC) will involve the following individuals:

- [redacted] (Medical Expertise) – Institute of Creative Technologies, USC
- [redacted] (VR in Pain Expertise) – College of Engineering at U of Washington
- [redacted], PT M (Psychology Expertise) – Ottawa Hospital Rehabilitation Centre

This is a multi-site clinical trial involving low risk. The individuals listed above, along with Dr. Simons and the Institutional Review Board (IRB), will be responsible for the duties involved with this data monitoring.

Conflict of Interest for Monitoring Bodies. Members of the SMC will have no direct involvement with the PI or the administration of the intervention. Each member will sign a Conflict of Interest (COI) Statement which includes current affiliations, if any, with any steering committees or advisory councils associate with study, pharmaceutical, and biotechnology companies (i.e. stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associate with commercial or non-commercial interests pertinent to the study objectives.

Protection of Confidentiality. Only de-identified and re-coded data will be presented during open sessions with the SMC. All data, whether in a report or discussed during SMC meetings are kept confidential. Participant identities will be kept confidently unless there are serious safety concerns in which the PI and SMCs involved may request and necessitate the identification of some or all data.

Monitoring Entity Responsibilities. The following are details of members of the study monitoring entity's responsibilities:

- ***Review of Study Documentation***: The CRC will be responsible for reviewing the Data Safety Monitoring Plan (DSMP), informed consent/assent documents, protocol amendments, and updates to the Manual of Operating Procedures (MOP) and Clinical Protocol for this trial on a weekly basis. The CRC will notify the PI immediately with any PDs and approvals for amendments to the protocol. The PI will have access to all these documents at all times and will be responsible for meeting with the SMC on a quarterly basis.

- ***Subject Accrual***: Review of subject accrual rates and compliance with inclusion/exclusion criteria will be conducted by the PI and SMC on a quarterly basis to ensure a sufficient number of participants are enrolled, properly screened for eligibility, and targeted goals outlined in the grant proposal are being met.

- ***Enrollment***: Review of the status of enrolled subjects will be monitored on a regular basis by the CRC and the PI. Quarterly updates will be monitored by the PI and SMC to ensure target enrollment is being met per grant proposal. Monthly enrollment reports will be provided to the NIAMS via NCR by the CRC.

- ***Adherence Data***: Data on adherence to treatment protocol will be collected on a weekly basis by the CRC and reviewed quarterly by the PI and SMC.

- ***AEs and Rates***: Adverse Events and the rate of occurrence will be tracked and noted per occurrence and the PI will be notified. Unless indicated necessary, AEs will be reviewed quarterly by the PI and SMC.

- ***SAEs***: Serious Adverse Events will be monitored in real-time and the PI will be notified within 24 hours of occurrence by the treatment team. The PI, SMC, NIAMS/NCR, and IRB will review this SAE and take appropriate action for the safety of the patient. It will be evaluated at the time of occurrence whether the participant will be withdrawn from the study.

- ***PDs***: Major PDs will be communicated to the PI immediately. All events will be communicated to the NIAMS via NCR within 48 hours of the PI becoming aware of the event.

8. INTERVENTION DISCONTINUATION

Patients and their parents have the right to withdraw consent/assent or discontinue participation at any time without penalty or any impact on the child's care. Because this is an exploratory clinical

trial, we will not discontinue participation based on missed attendance to treatment sessions. There will be no temporary discontinuations from treatment or study participation. The PI may withdraw a patient/parent dyad from the study for one or more of the following reasons:

- Failure to follow instructions of the PI or study staff.
- The PI decides that continued participation would be harmful (e.g., patient reports increased emotional or physical distress from exposure therapy)

Patients and parents will be asked permission to use data collected form the study if they are asked to discontinue or decide to withdraw from the study.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

To characterize feasibility of a future hybrid effectiveness-dissemination trial of PRVR in routine physiotherapy practice. Hypotheses: *PRVR participants will have (1) high patient-reported treatment satisfaction and high clinician-rated patient engagement scores; Clinicians will report high clinical proficiency and self-efficacy in using PRVR.*

Analysis Plan: *Satisfaction.* We will examine mean satisfaction scores, clinician rated engagement scores, and clinician proficiency and efficacy with PRVR clinical use. *Adherence/retention.* We will examine mean adolescent adherence to survey completion, percent of patients who dropout prior to treatment completion, and VR side effects reported. *Health care costs and pain medication use.* We will examine health care and pain medication use by calculating totals via healthcare cost surveys and compared across timepoints.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

The majority of the research data, including self-reported questionnaires, informed consent forms, appointment tracking, case report forms, adverse events, serious adverse events, protocol deviations, and unanticipated problems will be sourced and captured electronically by participant via REDCap. If participants opt to complete daily diaries, daily check-in surveys will be collected electronically by participant via LifeData. Data collection will occur either in-person on an encrypted study iPad, or at home via electronic surveys.

REDCap's features include research data collection instruments (surveys and forms), and an e-Consent Auto-Archiver Framework. The e-Consent Framework platform will be used to consent patients on site using a computer-based consent form rather than traditional paper documentation.

LifeData is a mobile application to collect experience sampling, ecological momentary assessment, and electronic check-ins. This app will be used to easily push notifications to child and parent devices to collect Daily Check-in data.

Word document versions of the REDCap data collection instruments can be found in the MOP Supplemental Materials Section:

Supplemental Materials I: Electronic Case Report Form (eCRF) Templates
Supplemental Materials II: Research Consent and Assent Forms
Supplemental Materials III: Self-Reported Questionnaires

The CRC will be responsible for maintenance of all data collection forms, and will include any updates in the monthly report to the NIAMS via NCR.

10.2 Data Management

All questionnaire data collected for the study will be exported into SPSS, SAS or R via REDCap. Treatment session audio/video recordings may be recorded digitally and saved on the secure, private drive on the server and only personnel associated with the study will have access to the files.

10.3 Quality Assurance

10.3.1 Training

Stanford University uses the "CITI" training program (Collaborative Institutional Training Initiative; https://www.citiprogram.org/). All staff must pass required tests on each module. A refresher course must be passed every 3 years.

Per NIH requirements, all staff will be trained in Good Clinical Practice (GCP), consistent with principles of the International Conference on Harmonisation (ICH) E6 (R2). The CRC will be responsible for maintaining documentation of all CITI and GCP training certifications.

An outpatient team of licensed Physical Therapists at each clinical site will provide study intervention sessions, trained in this modality of treatment by Laura Simons, PhD with ongoing consultation from Amy Weisman PT, DPT (expert in physical rehabilitation for chronic pain) and Maria Menendez, MD (expert in virtual reality intervention administration).

The PI will be responsible for and oversee all training of research personnel in GCP and the delivery of study interventions. All members of the research team will be trained on the contents of this document (MOP) and relevant study materials prior to beginning work on the study.

The PI and CRC will hold primary responsibility for study data quality control. To address quality control methods, all data will be entered into REDCap using standardized electronic case report forms (eCRFs).

10.3.2 Quality Control Committee

The PI and research coordinator will be hold primary responsibility for study data quality control. To address quality control methods, chart data will utilize standardized collection forms. For data entry of study information, a portion of files will be re-entered by a separate person, to check for consistency. If consistency is low, the entire data set will be re-entered.

10.3.3 Metrics

All self-report outcome measures have demonstrated psychometric soundness, including reliability and validity.

10.3.4 Protocol Deviations

Each protocol deviation (PD) will be captured and documented, by participant, in the Protocol Deviation Tracking Log eCRF (MOP Appendix E). All PDs will be collated and reviewed by the CRC and study PI.

A major protocol deviation or violation includes any procedure that differs from the IRB-approved protocol that was intended to eliminate an immediate hazard to the participant, was harmful, or is possible serious or continue non-compliance by a study staff member.

Major protocol deviations will be communicated to the PI immediately. All events will be communicated to the NIAMS via NCR within 48 hours of the PI becoming aware of the event.

Protocol deviations/violations that occur but do not affect participant safety will be submitted as part of the quarterly reports distributed to the SMC and subsequently shared with the NIAMS.

10.3.5 Monitoring

The study will be monitored by the research coordinator regularly throughout the collection of data. Oversight of this clinical trial is provided by the Principal Investigator (PI), Dr. Simons and a Study Monitoring Committee (see section 7.6).

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (MOOP Supplemental Materials II) and any subsequent modifications will be reviewed and approved by the Stanford IRB responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each parent participant, and a signed assent form for each child participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record. Per IRB requirements, any participant who turns 18 years of age while actively enrolled during the course of study will be contacted and consented as an adult.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIAMS, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIAMS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Steering committee – Study PI, Co-Investigators, and Research Coordinator for this study will meet monthly to discuss study progress relative to milestones, coordinate efforts, and review any protocol deviations or other issues requiring adjustment.

Safety Monitoring Committee – The Study PI and Study Monitoring Committee (Section 7.6) will meet quarterly to review study accrual, status of enrollment, adherence to data regarding study visit and intervention, and adverse events.

13. PUBLICATION OF RESEARCH FINDINGS

As an NIH-funded Clinical Trial this study will be registered at, and will submit summary results information to, ClinicalTrials.gov for public posting. Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee.

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