Project Identification and Abstract

1.1. * **Type of Submission**:

Research Protocol or Study on Human Subjects
Use of Humanitarian Use Device (Not Research)
Grant/Contract Only
Rely on another IRB (Ceded)
Right To Try

1.2. * **Full Title of Research Protocol**
At-Home Virtual Reality Guided Imagery Intervention for Chronic Pain

1.3. * **Short Title**
VR Guided Imagery for Chronic Pain

1.4. * **Abstract: Provide a simple explanation of the study and briefly address (in 1 to 2 sentences) each of the following points: rationale; intervention; objectives or purpose; study population or sample characteristics; study methodology; description of study arms (if appropriate); study endpoints or outcomes; follow-up; statistics and plans for analysis.**

Chronic pain affects over 100 million adults in the US, resulting in disability, loss of work productivity, and overall reductions in health, making chronic pain a major public health problem with an economic burden estimated at $560-635 billion annually. Opioids, the most frequently prescribed class of drugs to control pain, lack evidence supporting their long-term efficacy and carry a 15-26% risk of misuse and abuse among pain patients, highlighting a critical need to develop effective non-pharmacological interventions for pain. Guided imagery (GI), a cognitive-behavioral technique for guiding patients to create multisensory, imagined scenes to increase well-being, is an effective non-pharmacological intervention for reducing pain. However, its effectiveness is limited by patients imaging abilities. The long-term objective of this project is to reduce chronic pain and opioid use by developing an at-home virtual reality (VR)-GI intervention to improve chronic pain management using the Limbix VR Kit. Given the enhanced immersiveness and interactivity of VR, VR-GI is expected to reduce pain and reliance on opioids, as well as improve functional outcomes and mood, compared to traditional audio-only GI and usual care. Specific aims of this Phase I application are to: 1) develop and add VR-GI intervention prototypes for chronic pain management to the existing Limbix VR platform, and 2) evaluate feasibility and usability of an at-home VR-GI intervention in a 2-week clinical trial and prepare for a larger subsequent clinical trial. Two 15-min VR-GI experiences that guide patients through psychoeducation, relaxation exercises, and interactive virtual worlds that allow them to control their experience of pain will be created and added to the Limbix VR platform for the intervention. To assess feasibility of an at-home VR-GI intervention, 36 patients with chronic pain (chronic back pain, CBP or complex regional pain syndrome, CRPS) will complete a 2-week intervention with at-home daily practice of VR-GI (n = 24) or audio-only GI (n = 12). Pre-post treatment measures of pain intensity, opioid use, functional outcomes, and mood will be collected. Intervention feasibility and patient satisfaction will be evaluated post-treatment via questionnaire and qualitative interview. Based on Phase I results, a Phase II randomized clinical trial will evaluate the efficacy of VR-GI in reducing pain and reliance on opioids in CBP and/or CRPS patients. This research directly addresses the need to improve pain treatment to prevent opioid use disorder.

1.5. Is this a clinical trial? [The NIH defines a clinical trial as a prospective research study to evaluate the effects of one or more interventions on health-related biomedical or behavioral outcomes.]

Yes No

Clinical Trials must be registered on clinicaltrials.gov. All study personnel on studies meeting the NIH definition of clinical trials are required to satisfy the Good Clinical Practice (GCP) education requirement.

1.5.1. Is this a study where the Principal Investigator designed the study, created the protocol, or is responsible for the scientific and technical direction of the study (regardless of funding source)?

Yes **No**

1.6. * Select which IRB you are requesting review from:

USC - Biomedical IRB
USC - Social Behavioral IRB
CHLA - Institutional Review Board (CHLA)

Select **"USC - Biomedical"** if you are conducting biomedical research activities which fall under FDA jurisdiction (drugs, devices, etc.).

Select **"USC - Social Behavioral"** if you are conducting social behavioral research activities (community/field-based research such as survey and interview procedures, etc. that are not FDA regulated.).

NOTE: IRBAs and designated reviewers (Chairs, Vice Chairs, etc.) are currently assigned to review applications based on the type of research conducted. **Selecting the incorrect board may result in a delay of the review process**; and the application may be returned for the correct review board to be selected.

1.7. * To the investigator's knowledge, does the Institution have financial and/or intellectual property interests in the sponsor or the products used in this project? *An institutional conflict may occur when a financial interest of the institution has the potential to bias the outcome of research conducted by its employees or students or to create an unacceptable risk to human subjects.*

Yes **No**

2. Study Personnel

2.1. Study Personnel and their roles:

	Last Name	First Name	Organization	Study Role	Certifications	Obtain Consent	Interact with Participants	Access Identifiable Data	Manage Audit Access to PHI/ePHI (CHLA Only)
View	Richeimer	Steven	ANESTHESIOLOGY	Principal Investigator	HS GCP HIPAA	no	yes	yes	

View	Weinstein	Faye	ANESTHESIOLOGY	Co-Investigator	HS GCP HIPAA	no	yes	yes
View	Junghaenel	Doerte	CENTER FOR ECONOMIC AND SOCIAL RESEARCH	Data Analyst/Statistician	HS GCP HIPAA	no	no	yes
View	Yao	Iris	KECK SCHOOL OF MEDICINE	Data Analyst/Statistician	HS GCP HIPAA	no	no	yes
View	Zhang	Yao-Ping	ANESTHESIOLOGY	Research Coordinator	HS GCP HIPAA	yes	yes	yes

Who may be included as "key personnel" on an IRB submission?

Key Personnel are individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol. Individuals who should be named on an IRB application are those who engage in the following:

a. conducting research through an interaction or intervention with human subjects for research purposes
b. participating in the consent process by leading it or contributing to it
c. directly recording or processing identifiable private information, including protected health information, related to those subjects for the purpose of conducting the research study

Who should NOT be listed as key personnel on an IRB submission:

Individuals paid by the institution to perform a service not part of or paid by the research project performing services that are typically performed for non-research purposes or fee for service:

- honest broker
- pharmacy employees dispensing investigations drugs
- hospital employees obtaining blood through a blood draw or collect urine and provide such specimens to investigators as a service
- radiology clinic employees performing chest x-rays and sending results to investigators as a service
- routine laboratory analyses of blood samples for investigators as a commercial service
- transcription of research study interviews as a commercial service
- not administering any study intervention being tested or evaluated under the protocol

2.2. Is the Principal Investigator a staff member, student, resident, fellow, postdoctoral scholar, other trainee, visiting scholar, or visiting faculty member at USC/CHLA?

Yes **No**

2.4. Does your study include specific aims or endpoints that relate to cancer risk factors, cancer screening or diagnosis, cancer prevention, cancer treatment, or supportive care?

Note: For studies of diet, tobacco, sun exposure, or other cancer risk factors, or any study that includes cancer patients, please answer yes.

Yes **No**

2.5 Specify the group/organization who has reviewed this study for scientific merit:

.

Federal Agency (e.g. FDA, NIH, CDC, DOE, NSF, DOJ, etc.)
USC Norris Clinical Investigations Committee
Doctoral Dissertation Committee
Other
None

4. Funding Information

4.1. * **What existing or pending support will be used for this study?** (check all that apply)

- Cooperative Group (SWOG, COG, RTOG, etc.)
- CTSI
- Departmental/Institutional Funds
- Federal Grant/Contract
- Non-Profit (including Foundations and Universities)
- Industry
- Intramural/Internal Grant
- State or Local Grant/Contract
- No Funding
- Other
- **Subcontract from another institution**

Change of existing/addition of new funding sources and agencies will require an amendment.

4.1.1. Will you be submitting an Urgent Review request?

Yes No

4.1.1.1. Please attach a document that supports your Urgent Review request:

JIT Info(0.01)

4.1.2. Will any funds come from the National Institutes of Health (NIH)?

Yes No

4.2. If the funding source has undergone separate review by the IRB (i.e., cooperative group grants, umbrella grants, multi-project/program grants, center grants), try to select it from the list using the "Add" button. If the funding source is not displayed in the list, enter the information in question 4.4.

Grant #	Principal Investigator	Grant Title

There are no items to display

4.2.1. If the grants selected in question 4.2 fund multiple studies, please attach the specific pages of the grant that are relevant to THIS study.

Name	Version	Modified

There are no items to display

4.4. Add the details of each source of funding for this study.

	Sponsor	Principal Investigator	Type of Funding
View	National Center for Medical Rehabilitation Research at the Eunice Kennedy Shriver National Institute of Child Health & Human Development and the Center for Translation of Rehabilitation Engineering Advances and Technology	Richard Greenwald	Federal: Center Grant *
View	National Institutes of Health	Benjamin Lewis & Steven Richeimer	Federal: Grant *

4.5. If there are related awards or proposals, please use the respective button below to link it to this study.

Related Proposals from Cayuse (uncheck to remove):

Proposal Number	Project Title	Principal Investigator	Sponsor	Proposal Start Date	Proposal End Date	Status Name

There are no items to display

Related Awards from Cayuse (uncheck to remove):

Award Number	Project Title	Principal Investigator	Sponsor	Award Start Date	Award End Date	Status Name

There are no items to display

5. Type of Study Review

5.1.	Select the type of review that you are

requesting for this study:

Full Committee Review
Expedited Review
Exempt Review
Coded Specimens/Data

5.2.

All studies require a fully developed protocol. For investigator-initiated studies, use the appropriate protocol template (Social Behavioral, Biomedical, Secondary Analysis Protocol located at the OPRS/IRB website, or the Cancer Center Protocol located at the CISO website). If you are unsure which protocol template to use, please consult with the IRB prior to developing your protocol. Use of an incorrect protocol will result in the application being returned as incomplete.

****Please note that a grant application cannot serve as the protocol.****

Attach the protocol below.

Name	Version	Modified
There are no items to display		

5.3. Attach the sponsor's template informed consent here.

Name	Version	Modified
There are no items to display		

5.4. If any study documents are password protected, enter the passwords here.

5.5. If there is a sponsor protocol number associated with this file, specify it here:

6. Study Locations

6.1. Identify the locations where the research activities described in this application will be performed (check all that apply):

USC HSC - Health Sciences Associated Locations
USC UPC - University Park Associated Locations
CHLA
LAC+USC Associated Locations
Other

6.3. Will any research activities be conducted at any other site not affiliated with USC or CHLA?
Yes **No**

6a. HSC Location(s) and/or LAC+USC Locations

This screen is required if you indicated HSC - Health Sciences Associated Locations or LAC+USC Associated Locations (Question 6.1.)

6a.1. Locations that recruitment, consent, and/or study procedures will be performed: (check all that apply)

Location
LAC+USC Medical Center
LAC+USC Emergency Dept
LAC+USC Outpatient Clinics
LAC+USC 5P21 Building

Keck Hospital of USC Facilities
USC Norris Comprehensive Cancer Center Facilities
Keck School of Medicine of USC
USC Center for Health Professions (CHP)
USC School of Dentistry
Verdugo Hills Hospital
Other location (e.g., subjects home, community)

6a.1.1. Describe other location(s):
participants consented in their homes via internet

9. Methods and Procedures - Selected Descriptors/Community Engaged Research

Note: The list of items below IS NOT an all-inclusive list of methods and procedures available to investigators. The list only includes items that will trigger additional questions specific to areas of research or are necessary for the review process.

9.1. **NOTE:** Review the information under the blue question mark before answering this question.
The study procedures involve interactions or interventions with participants (e.g., medical procedures, online surveys, in person interviews).
Secondary Analysis: This study involves use of data/specimens **that have been or will be collected/generated for non-research purposes** (e.g., medical records, student records).
Secondary Analysis: This study involves use of data/specimens **that have already been collected/generated for another research purpose** (e.g., existing research datasets, existing specimens collected for research).

9.2. Study Procedures: (check all that apply)

Audio/Video Recordings or Photographs
Behavioral Observations and/or Behavioral Experimentation
Behavioral Interventions
Deception
Interview/Focus Groups
Population-based Field Study
Psychophysiological Testing
Surveys/Questionnaires/Psychometric Testing

Anatomic Pathology Specimens
Approved/Investigational Devices
Approved/Investigational Drugs and Biologics
Biohazardous Substances (e.g. fresh tissue or tissue fluids, infectious agents, microorganisms, recombinant DNA, or shipment of biological material)
Blood Collection
Controlled Substances
Creation of a Data or Tissue Repository
Emergency Research (with exception from informed consent requirements)
Gene Transfer Study
Heritable Genetic Specimens or Germ Line
Magnetic Resonance Imaging (MRI) or ultrasound other than clinically indicated
Radiation Exposure Other Than Clinically Indicated Tests and/or Therapy (e.g. x-ray, CT, DEXA, radiation therapy, etc.)
Stem Cells or Cell-Based Therapy
Substance Abuse Treatment (with medication)
Other Medical Procedures/Considerations

9.5. Will data from this study be subject to the NIH Genomic Data Sharing (GDS) policy?
Yes **No**

9.6. Does your study involve community-engaged research (community-engaged research addresses community needs and involves the community in research plan, conduct of study, etc)?
Yes **No**

9.7. Will data from this research be submitted to the US Food and Drug Administration or will data be held for inspection by the FDA?
Yes No

10. Characteristics of the Study Subject Population

10.1. What is the maximum number of subjects you plan to recruit for this site? (Integer values only)
36

10.1.1. If this is a multi-site study, indicate the projected total subject accrual. (Integer values only)

10.1.2. If necessary, provide further explanation of accrual goals for all subject populations.
36 will be recruited for 2 week at-home intervention feasibility testing.

10.2. Describe the inclusion criteria for enrollment. **(Refer to specific sections of the protocol/grant, if applicable)**
- English Fluency
- Diagnosis of chronic back pain or complex regional pain syndrome
- Average pain intensity of 5 on a 0 to 10 scale for more than 3 month
-Access to a device with video and audio capability and sufficient WiFI to participate in on-line sessions

10.3. Describe the exclusion criteria for enrollment. **(Refer to specific sections of the protocol/grant, if applicable)**
- History of significant motion sickness
- Active nausea/vomiting
- Epilepsy
- Significant movement problems
- Significant vision or hearing impairment

10.3.1. If there are any age, ethnic, language, or gender-based exclusion criteria, please provide justification.
Children and adolescents under 18 years of age will not be included as this study is specifically designed to address adult chronic pain. Changes to the intervention design beyond the scope of the present study would be warranted for children and adolescents due to cognitive and developmental differences between children and adults. These differences preclude the applicability of the proposed intervention to children. A separate, age-specific study on virtual reality (VR) guided imagery for chronic pain in patients under 18 years old is preferable to their inclusion in the present study. Additionally, the long-term effects of extended VR exposure on children and adolescents are largely unknown and thus these groups are excluded from the present study to mitigate possible risks.

11. Research Objectives and Background

11.1. Describe the specific objectives or aims of the study and hypotheses or research questions. (R*efer to specific sections of the protocol/grant, if applicable*)
Specific Aim 1. Develop and add VR-GI prototypes for chronic pain management to the existing Limbix VR platform. VR-GI prototype development will involve creating narrative scripts and audiovisual content. VR-GI experiences will guide patients through pain management education and relaxation exercises within interactive virtual environments that allow them to control their experience of pain. A protocol for the VR-GI intervention will also be created. SA1 Milestone: Completion and addition of two 15-minute VR-GI prototypes and a VR-GI intervention protocol to the Limbix VR platform.

Specific Aim 2: Evaluate feasibility and usability of at-home VR-GI intervention in a 2-week clinical trial and prepare for larger subsequent clinical trial. 36 patients (chronic back pain or complex regional pain syndrome, CRPS) will be recruited to complete 1-2 online clinic training sessions followed by 2 weeks of daily at- home VR-GI (n = 24) or traditional audio-only GI (n = 12) practice. Intervention feasibility will be evaluated via questionnaires and via informal interviews with providers. Pre- and post-intervention measures of opioid use, pain ratings, functional outcomes, mood, and quality of life will be collected. Daily pre- and post-GI practice pain ratings will be collected to evaluate potential habituation effects of VR-GI over time. SA3 Milestone: Using a confidence interval approach, demonstrate that the VR-GI

intervention is feasible, defined as meeting an 80% threshold for feasibility metrics (i.e., enrollment feasibility, intervention tolerability, and compliance). Efficacy, defined as a 30% reduction in pain ratings and standardized effect sizes between 0.3- .05 on opioid use and other collected measures, will also be evaluated to prepare for a Phase II clinical trial.

11.2. Provide a summary of the background of the study, and explain how this research will contribute to existing knowledge. Describe previous work that provides a basis to show that the proposed research can be carried out without undue risk to human subjects. Include relevant citations. (*Refer to specific sections of the protocol/grant, if applicable*)

Public health impact of chronic pain

Chronic pain, typically defined as pain lasting for at least 3 months, is a critical problem affecting millions of Americans with huge economic, societal, and individual repercussions. The US economic burden of chronic pain in terms of lost work productivity and healthcare is estimated at $560-635 billion annually [1], with the average chronic pain patient seeking treatment for 7 years [2]. Chronic pain increases the incidences of anxiety and depression and is a major predictor of decreased quality of life and increased disability [1]. The chronic pain problem in the US is inextricably linked to the opioid epidemic, as opioids remain the most prescribed drug for pain. The goal of this research is to develop, evaluate, and ultimately, commercialize a novel non-pharmacological virtual reality (VR) guided imagery (GI) intervention for reducing chronic pain. It is anticipated that effective non-pharmacological pain management will reduce reliance on opioids and thus help prevent opioid use disorder.

The research proposed in this application will capitalize on a research foundation that supports the effectiveness of non-pharmacological interventions, in general, and GI, specifically, for chronic pain management, as well as on existing evidence that VR enhances the efficacy of cognitive-behavioral treatments and is effective in managing pain. Below, this research is summarized and the unique contributions of the proposed project to improving chronic pain patient care and managing opioid use are described.

Opioids are associated with myriad problems for chronic pain patients

The use of opioids for chronic pain treatment is controversial for many reasons. Up to 80% of individuals prescribed opioids experience harmful side effects [3], including nausea, decreased cognitive function, and decreased psychomotor coordination [4]. Long-term use of opioids has also been associated with more serious adverse drug events, including cardiovascular events, fractures, and sexual dysfunction, which are costly in terms of increased length of stay, readmissions, and inpatient mortality [4]. Perhaps most seriously, opioids have a high risk of misuse and abuse; 15%-26% of chronic pain patients misuse or abuse prescribed opioids [5] and an estimated 70% of all prescription drug overdoses in the US are due to opioids [6]. Recent reductions in opioid prescribing by physicians has led many individuals to seek out illicit opioids, resulting in an increase in opioid deaths from heroin and fentanyl [7]. Up to 80% of new heroin users previously misused prescription painkillers [8].

Equally troubling is a lack of evidence demonstrating the long-term effectiveness of opioids for chronic pain [9, 10]. Even in studies reporting reductions in chronic pain by opioids, the average reduction is only ~32%16. At the same time, long-term use can lead to tolerance or even hyperalgesia17, which often result in increased prescribed or consumed dosages. However, increasing dosages do not increase pain relief [9] but do increase overdose risk18. The lack of support for long-term efficacy and the concomitant risks of opioids for chronic pain patients clearly indicate a need for alternative or complementary interventions to reduce opioid use and the risks of opioid use disorder. Indeed, CDC guidelines for prescribing opioids for chronic pain explicitly state: "nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain."

Non-pharmacological interventions effectively reduce chronic pain

Government agencies have advocated for the use of non-pharmacological interventions for chronic pain management [11, 12]. Studies have demonstrated the effectiveness of such interventions, which include acupuncture, yoga, meditation, and cognitive behavioral therapy, for reducing chronic pain and opioid use, and improving functional outcomes [13, 14]. Interdisciplinary pain management strategies, incorporating pharmacological and non-pharmacological interventions are cost-effective, reducing emergency room and primary care visits, pain medication use, and the number of sick days from work [15, 16]. Compared to pharmacological interventions, non-pharmacological interventions also have fewer adverse effects [13, 14].

Though the evidence supporting non-pharmacological interventions for chronic pain is promising, the widespread adoption of such interventions has been limited due to the low quality of investigations into non-pharmacological interventions for chronic pain [13, 14] and limited access to non-pharmacological interventions, as such interventions typically require staff or clinician training and time for effective delivery. The development of easily delivered, at-home solutions for pain management, requiring minimal staff or clinician training and time, would be of great value in advancing chronic pain management and reducing the risk of opioid abuse.

Guided imagery is an effective non-pharmacological intervention for chronic pain

GI is a cognitive-behavioral technique in which individuals are instructed through guided narration to create sensory-rich images in their mind to alter their psychological and physiological states with the goal of reducing their experience of pain. The advantages of GI for chronic pain management are numerous. GI interventions have shown medium to large effect sizes for pain reduction and functional outcomes [17-21], indicating that such interventions are a promising treatment option. GI has also been shown to improve mobility [22], quality of life [17, 20, 23, 24], mood [18, 20], and self-efficacy for managing pain [25, 26]. It has been shown to reduce pain medication use [22, 27] and visits to care providers [17]. Though not all non-pharmacological interventions are efficacious or appropriate for all subpopulations of pain patients [13, 14], there are few, if any, contraindications for GI and its acceptability and effectiveness has been demonstrated across disparate pain populations, including patients with osteoarthritis [22, 28], chronic tension type headaches [29], fibromyalgia [25, 26, 30, 31], abdominal pain [17, 32], and cancer pain [18, 23, 33-36]. Adverse events, both serious and minor, are rarely reported. GI is also a cost effective and accessible form of long-term pain management, as it has traditionally been practiced at home with audio recordings. It thus doesn't take up valuable clinician or staff time and is easy for patients to practice with little equipment necessary. Finally, recent neural evidence indicates that GI reduces pain via an opioid-independent mechanism [37], indicating that GI could provide additive pain reduction over and above that of opioids. This evidence also supports the use of GI for patients for whom opioid-mediated pain pathways are compromised, as may be the case for individuals who have developed opioid tolerance or hyperalgesia.

Despite these advantages to using GI for managing chronic pain, limitations in present GI approaches exist. Critically, GI depends on the ability of patients to imagine vivid experiences in their mind. Individual differences in imaging abilities can therefore affect the success of GI in reducing pain [23, 33-35, 38], increasing variability in treatment response and reducing the potency of this intervention for many patients. Additionally, when GI is performed at-home, it has traditionally been delivered via audiotape or CD. Such delivery methods make it difficult for physicians to adequately track patient compliance. Furthermore, meta-studies of GI indicate that research trials have lacked scientific rigor in terms of small sample sizes, lack of proper control conditions, and failure to report effect sizes [39-43]. Given the critical need for easy to deliver, effective non-pharmacological interventions for chronic pain across large and diverse subpopulations of patients, more rigorous evaluations of GI and its generalizability across pain populations are warranted.

VR is effective and advantageous for reducing psychological symptoms

Existing research supports the efficacy of VR for changing attitudes and behaviors [44-46], supporting the potential for VR to change attitudes/behaviors around opioid use and chronic pain. VR is also effective in reducing psychological symptoms of behavioral health disorders, as evidenced by decades of research demonstrating that VR exposure therapy, wherein patients are virtually exposed to the things they fear, equivalently reduces psychological symptoms compared to in vivo exposure in patients with anxiety, phobias, and PTSD [47-50]. Available evidence also shows that VR experiences generalize more readily to the real world [51] and are more effective [51, 52] in reducing symptoms compared to imaginal exposure, supporting the superiority of VR over therapies that rely on mental imagery. These benefits of VR are thought to derive from a greater sense of presence-- the feeling of "being there"-- driven by immersive sensory experiences [53, 54].

VR interventions are superior to alternative treatments in a number of other ways as well. Patients have reported preferring VR interventions [55, 56] and providers have indicated that they are simpler and more practical [57] than other forms of treatment. VR treatments can also be effectively delivered at home [58, 59] and thus, if appropriately scaled, could increase accessibility of mental health resources and reduce burdens on clinician time, particularly in areas where mental health resources are limited or in high demand. VR is thus likely to be an effective medium for improving the efficacy of cognitive-based pain solutions and effecting behavioral change.

VR interventions are effective in reducing pain

VR seems particularly effective for pain-related interventions. Theoretical perspectives suggest that VR reduces pain via top-down modulation of pain pathways by cognitive and emotional brain regions [60]. Pain perception requires attention, which is a limited cognitive resource, thus diversion of attention from pain is believed to mechanistically account for how distraction reduces pain [61]. Evidence that active VR experiences more effectively reduce pain than passive VR experiences [62] supports this idea, as active VR experiences engage more attentional resources than passive ones. Immersive, multisensory VR experiences that heighten the sense of presence in a virtual environment also engage emotional regions of the brain. Given evidence that positive emotions decrease pain [63], the influence of emotional regions on pain pathways may be a second mechanism by which VR experiences modulate pain. Preliminary neuroimaging evidence supports modulation of pain-related brain activity by VR experiences [64].

VR has mainly been used as distraction from acute pain such as in burn victims [65], cancer patients [66], and dental pain patients [67]. A recent meta-analysis found large effect sizes for immersive VR distraction in acute pain reduction [68]. During acute pain, VR distraction has also been shown to reduce opioid use [69], anxiety [70], time spent thinking about pain [71], and estimates of elapsed time [66]. Cost analysis models suggest that VR therapy for pain can be cost effective, particularly if it reduces length of stay [72]. Importantly, the effects of VR on acute pain do not appear to habituate across multiple sessions [73, 74], suggesting that VR interventions can effectively modulate pain over time and thus supporting the potential for VR in chronic pain management.

Despite a large and growing literature on VR and acute pain, little research has focused on the effects of VR on chronic pain, though preliminary evidence is promising. After single sessions of VR, chronic pain patients, including those with chronic regional pain syndrome (CRPS) and back pain, have reported reductions in pain up to 60% [75-78], as well as increased motor function [76, 77]. Few studies have examined multisession VR protocols or long-term effects of VR interventions for chronic pain, but, for example, a pilot study by Sato et al [79] found that interactive VR completed over 5-8 weekly sessions resulted in >50% reductions in pain intensity in 4 out of 5 CRPS patients, supporting the potential for VR to produce clinically significant changes in chronic pain.

Though encouraging, there are clear gaps in the literature on the efficacy of VR in reducing chronic pain. First, most studies on chronic pain to date have evaluated VR effects on chronic pain in a single VR session. Such studies indicate that chronic pain can be modulated by VR experiences, but the potential for a longer course of VR treatment to induce sustained reductions in chronic pain requires further investigation. Second, VR interventions have almost exclusively been conducted in clinic or laboratory settings, requiring valuable staff or clinician time and making such interventions difficult to feasibly incorporate into provider workflows. Evaluation of whether at-home VR practice can effect meaningful changes in chronic pain and the feasibility of such an intervention for both patients and providers is warranted. Third, although stable effects of VR on pain have been demonstrated in healthy individuals and individuals undergoing repeated acutely painful procedures, replication of such findings in patients with chronic pain is still necessary. Finally, further research is necessary to determine whether VR therapy for chronic pain can replace or reduce opioid use.

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12. Methods and Procedures - Prospective Studies

12.1. Describe in detail the design and methodology of the study. Provide a detailed description of the planned data collection, specific outcomes, and criteria for evaluation and endpoint definition. If applicable, include information on stratification or randomization plans. Include the frequency and duration of each activity and the total length of subject participation. Identify and distinguish between those procedures that are standard of care and those that are experimental. (*Refer to specific sections of the protocol/grant, if applicable. Describe any differences between the protocol and the local site.*)

Specific Aim 1: Develop and add VR-GI prototypes for chronic pain management to the Limbix VR platform.
R&D efforts will include creation and integration of the VR-GI prototypes to the existing Limbix VR platform. This process will be overseen by Limbix CEO, Mr. Benjamin Lewis. A number of ideas for content development will be created by the Limbix team and reviewed with Dr. Steven Richeimer and Dr. Faye Weinstein at USC. From this list, two ideas will be chosen and developed further to create two 15-minute VR-GI prototypes. The development of these experiences will involve creating narrative scripts based on traditional GI audio recordings and designing audiovisual computer-generated VR content to accompany the GI narration. The narrative scripts will include psychoeducation content that explains how the mind and brain can influence physical pain and how they can be trained to effect changes in experienced chronic pain. Narration will guide users in breathing and relaxation exercises and explain how patients can continue to exert

control over their pain outside of the VR-GI experience. Narration will also help patients navigate and interact with their virtual environment during the VR-GI experiences. Narrative scripts for an audio-only GI active control condition for the clinical trial proposed in SA3 will also be developed. These will mirror those of the VR-GI prototypes, guiding participants to imagine the actions, imagery and sounds that will be directly experienced in the VR-GI intervention.

Virtual scenes will take participants on adventures through aesthetically pleasing environments that provide patients with the opportunity to visualize their pain and, critically, give them the ability to control (i.e., reduce) their pain. The exercise of imagining a reduction in their pain will be accompanied by audiovisual imagery in VR. As an example, a VR-GI experience might involve searching for a magic wand that, when found, can be pointed at the part of a virtual body where patients feel pain; patients will see a visual representation of their pain and will watch it change in VR after using the magic wand. Another VR-GI experience might involve entering the "brain's control room" where patients can choose a lever to turn down their pain level, which will be represented in the virtual environment and altered by the act of using the lever. Users will be able to navigate and interact with VR content using a controller, head motion, gaze control, and/or voice control to manipulate elements of the virtual environments. All of these methods of interacting with virtual scenes have been tested and are functional on the existing Limbix VR platform.

Specific Aim 2: Evaluate feasibility and usability of VR-GI experiences based on patient and provider feedback.
After the two VR-GI prototypes have been developed and integrated onto the Limbix VR platform, 4 chronic pain patients (2 with chronic back pain, CNBP, and 2 with complex regional pain syndrome, CRPS) will be recruited for initial feasibility and usability testing of the experiences. Four providers from the USC Pain Center will also be informally recruited to give feedback on the VR-GI experiences. Patients and providers will view both VR-GI experiences (each 15 minutes long) and complete a qualitative interview conducted by a trained USC research coordinator. Patient views on feasibility and usability will be evaluated via questions pertaining to ease of use, comfort, willingness to use again, enjoyment of the experience, and perceived feasibility of the proposed at-home intervention protocol and integration in daily routine. Provider views on feasibility and usability will be evaluated via questions pertaining to ease of use and willingness to use in their practice, perceived potential for the proposed intervention to improve patient outcomes, and perceived feasibility of integrating the proposed intervention into their workflow. Feasibility questionnaires will be developed by Dr. Lake in collaboration with Dr. Richeimer. Iterative changes to VR-GI prototypes and intervention protocol will be made according to feedback received. Additional feedback will be sought, if necessary, until the VR-GI experiences and proposed protocol are deemed acceptable to providers and patients and project PIs. Patients will be compensated for their time.

The Limbix VR Kit was initially designed such that a clinician would use the tablet to select content and relevant settings for a patient to experience in VR. Patients' abilities to use the Limbix VR Kit without the help of research staff will also be evaluated to ensure that the VR-GI intervention can be easily delivered at home. Changes to the user experience will be made to improve usability, if necessary.

Specific Aim 3: Evaluate feasibility, usability, and preliminary efficacy of a 2-week VR-GI intervention clinical trial.
Participants & Procedures: 36 chronic pain patients (18 with chronicback pain, CBP, and 18 with complex regional pain syndrome, CRPS) with no significant movement problems will be recruited from the USC Pain Center by referring physicians. Chronic pain will be defined as an average pain level of 5 or greater on a 0-to-10 pain intensity scale for greater than 3 months. Patients will be individually randomized to the VR-GI condition (n = 24, 12 CBP and 12 CRPS) or the audio-only GI active control condition (n = 12, 6 CBP and 6 CRPS). After informed consent and eligibility screening, all patients will complete pre-assessment questionnaires, an individual training session for completing VR-GI using the Limbix VR Kit or audio-only GI using an mp3 player, and their first session of GI. Patients will be instructed to practice GI at home once per day for 2 weeks. After 2 weeks, patients will be contacted to complete post-assessment questionnaires and a qualitative interview regarding intervention feasibility and acceptability. Referring physicians will also be informally interviewed regarding feasibility of integrating the intervention into their workflows. To ensure results are unbiased, a USC research coordinator with no commercial interest in the study outcome will conduct data collection.

Potential Problems: The Limbix team has extensive experience in product development and thus has first-hand knowledge of the problems that may be faced during the development of this product. Limbix has already solved many feasibility issues inherent in delivering a VR intervention for patients, as ascertained through extensive user research, via the development of the commercially available Limbix VR Kit. The usability and feasibility testing outlined above have been explicitly designed to expose issues early in the development process to help avoid unanticipated problems in product development.

One potential issue we foresee is whether patients will comply with at-home GI practice. Tracking compliance via the VR Headset will allow for the evaluation of this possibility. If compliance is found to be an issue with early study participants, strategies could be employed to encourage compliance, such as sending reminders, discussing with patients how to better integrate practice into their daily routines, or having patients directly report daily practice to the research coordinator to increase accountability. Tracking compliance objectively, rather than relying on subjective report, will not be possible for the audio-only GI group. Though this represents a limitation in the study design, it nevertheless reflects an advantage of using VR for delivering GI. Another potential problem is that patients may not return loaned equipment. To limit this possibility, participants will be financially incentivized to return equipment at the conclusion of the study. Patients will receive the equipment by mail to their address along with a pre-paid envelope to return the equipment. Finally, participants will be asked to use online surveys to report pain ratings before and after at-home GI practice, requiring that they have internet access at home. We expect that this will not be problematic for most participants. If necessary, participants can keep written logs of daily practice.

12.2. Describe the statistical considerations for the study, how the sample size was determined, and how the results will be analyzed, if applicable. (*Refer to specific sections of the protocol/grant, if applicable*)

Given that the goals of this study are primarily to demonstrate feasibility and to evaluate efficacy outcomes insofar as to prepare for a larger clinical trial, the sample size of this planned pilot study is small. Guidelines suggest that 12 participants per group are sufficient for pilot studies, as the gains in precision of point and variability estimates largely stabilize around this value. As per recommendations for pilot studies, formal hypothesis testing will not be prioritized in data analysis, as the small sample sizes in this proposed project will only allow for the detection of large effects. The sample size and planned data analysis, which will rely on qualitative and confidence interval approaches, are appropriate to accomplish the stated objectives of this clinical trial. A larger subsequent Phase II clinical trial will allow for a statistical comparison of VR-GI relative to usual care and active control conditions, such as audio-only GI and VR relaxation or distraction, over a longer intervention duration and a follow-up period.

For this clinical trial, we expect to enroll 36 patients with chronic pain (18 CNBP and 18 CRPS) of which 24 (12 CBP and CRPS) will be randomized to receive VR-GI and 12 (6 CBP and 6 CRPS) will be randomized to receive audio-only GI. Given that the goals of this study are primarily to demonstrate feasibility and to evaluate efficacy outcomes insofar as to prepare for a larger clinical trial, the sample size of this planned pilot study is small. Guidelines suggest that 12 participants per group are sufficient for pilot studies, as the gains in precision of point and variability estimates largely stabilize around this value. For all outcomes, effect sizes are expected to be medium to large.

To evaluate feasibility, outcomes of enrollment feasibility, intervention tolerability, and compliance will be qualitatively assessed. Additionally, confidence intervals will be calculated for each outcome measure using varying levels of confidence to evaluate the strength of preliminary evidence that the true value of the feasibility metric includes an 80% threshold. An 80% threshold for each outcome will be considered a conservative measure of feasibility. Feasibility and acceptability of the intervention will also be qualitatively evaluated based on post-assessment interviews with patients. Post-intervention patient interviews are expected to demonstrate that the at-home VR-GI intervention was feasible for patients to integrate into their daily routine, easy to use, and deemed acceptable and efficacious for pain management.

For efficacy measures, means, variability, and effect sizes for differences between pre- and post-intervention changes in pain intensity, pain medication use, functional outcomes, quality of life, and mood will be calculated. A confidence interval approach, using multiple levels of confidence to evaluate the strength of preliminary evidence, will be taken to evaluate whether the mean treatment difference is above zero and whether confidence intervals include a clinically important difference for each outcome. Pain intensity ratings will serve as the primary outcome measure in a follow-up Phase II clinical trial. The clinical significance for pain reduction will be considered 30%. For all other measures, clinical significance will be defined as a standardized effect size between 0.3 and 0.5.

Feasibility and efficacy measures will be descriptively compared between VR-GI and traditional audio-only GI. It is expected that feasibility of these two interventions will be comparable. Efficacy measures are expected to show larger effect sizes for the VR-GI experience. To evaluate the generalizability of VR-GI, whether there are notable differences in feasibility or efficacy between the two pain populations, CNBP and CRPS, using a confidence interval approach will also be evaluated. No such differences are anticipated. A larger subsequent Phase II randomized clinical trial will allow for

statistical comparisons between conditions (VR-GI and audio-only GI) and pain populations (CNBP and CRPS).

As the extant literature has yet to evaluate whether the short-term effects of VR on chronic pain are sustained across repeated sessions, the time course of daily pain intensity ratings pre- and post-GI practice will be plotted and assessed for evidence of habituation effects over time (accounting for anticipated changes in pre-practice pain ratings over time).

As per recommendations for pilot studies, formal hypothesis testing will not be prioritized in data analysis, as the small sample sizes in this proposed project would only allow for the detection of large effects. The sample size and planned data analysis, which will rely on qualitative and confidence interval approaches, are appropriate to accomplish the stated objectives of this clinical trial. A larger subsequent Phase II clinical trial will allow for a statistical comparison of VR-GI relative to active control conditions, such as audio-only GI, VR relaxation or distraction, and usual care over a longer intervention duration.

Measures & Analyses: Feasibility outcome measures will include enrollment feasibility (i.e., proportion of recruited participants ineligible to participate and/or who decline to enroll), intervention tolerability (i.e., proportion of enrolled participants who discontinue intervention, are lost to follow-up, or experience adverse events), and compliance (i.e., proportion of at-home daily practice completed). Compliance can be tracked via the VR Headset, which will log the time and duration of practice. Measures of pain ratings, pain medication use, functional outcomes, quality of life, and mood will be collected before and after the 2-week intervention. Daily pain ratings before and after GI practice at home will be collected via online surveys. Patient feedback on ease of implementation, satisfaction with technology and content, expressed willingness to continue use, and enjoyment will be assessed via qualitative interview. These questions will be developed by Dr. Lake in collaboration with Dr. Richeimer. Due to the small sample size of this feasibility study, statistical analyses will not be prioritized. Instead, qualitative analysis and confidence interval approaches will be taken (see Protocol Synopsis) to evaluate feasibility of the VR-GI intervention and to prepare for a larger Phase II clinical trial to evaluate efficacy. Exploratory qualitative analyses will assess whether daily reported pain reductions habituate over time, whether one of the VR-GI prototypes was preferred over the other, whether VR-GI differentially affected CNBP and CRPS patients, and whether sex, ethnicity or race affected outcomes. All data analysis will be conducted by Dr. Lake and supervised by project PI.

18. Methods and Procedures - Device Information

This screen is required if you indicated the use of Approved or Investigational Devices (Question 9.2.)

18.1. Fill in an entry for each device that will be used in this study.

Generic and Brand Names	Category of Regulation
Limbix Virtual Reality Guided Imagery	Abbreviated IDE - nonsignificant risk device

18.2. Attach a copy of any Investigators Device Brochures for the devices listed above.

Name	Version	Modified
Device Brochure(0.01)	0.01	7/15/2019 7:03 PM

18.3. Describe where the investigational devices will be stored, how they will be secured, and how the inventory will be managed.

Investigational devices will be kept at the USC Pain Center in a locked storage room out of direct sunlight. Limbix Health, Inc. will provide USC Pain Center with a maximum of 36 VR Kits for patient use. Only USC study personnel will have access to inventory and will be responsible for storing and securing the devices. They will be shipped to the participants address along with a pre-paid shipping envelope to return the device.

21. Methods and Procedures - Surveys/Questionnaires/Psychometric Testing

This screen is required if you indicated the use of Surveys, Questionnaires, or Psychometric Testing (Question 9.2.)

21.2. Attach copies of all measures/instruments that will be used for this study.

Name	Version	Modified
CRPS Severity Scale (CSS-17)(0.01)	0.01	7/16/2019 10:11 AM
Feasibility Testing Questionnaire(0.01)	0.01	7/16/2019 11:59 AM
Generalized Anxiety Disorder Scale(0.02)	0.02	7/16/2019 10:12 AM
Medication Use(0.01)	0.01	7/16/2019 10:12 AM
Numeric Pain Rating Scale(0.02)	0.02	7/16/2019 10:08 AM
Oswestry Disability Index- low back pain(0.02)	0.02	7/16/2019 10:09 AM
Oswestry Disability Index- neck pain(0.01)	0.01	7/16/2019 10:10 AM
Patient Health Questionnaire(0.02)	0.02	7/16/2019 10:10 AM
Short Form Health Survery(0.02)	0.02	7/16/2019 10:11 AM
Usability Testing Questionnaire(0.03)	0.03	7/16/2019 11:56 AM

22. Special Subject Populations

22.1. Indicate any special subject populations you intend or expect to enroll in the research: (check all that apply)

Healthy Volunteers Undergoing Clinical/Medical Procedures for Research Purposes

Employees or Students

Adults not Competent to Consent (or likely to lose the capacity to consent during the study)
Non-English Speaking Populations
Minors (subjects under 18 years of age)
Pregnant Women / Human Fetuses
Neonates (infants under 30 days old)
Prisoners/Detainees
Wards
Military Personnel
American Indian and/or Alaskan Native (AI/AN), Native Hawaiian and other indigenous communities
None of the above

23. Study Resources

23.1. Describe the time the investigators have available to conduct and complete the research and justify that it is sufficient. Please check-off the items that apply to this study.

Employed interns, residents, fellows, or postdocs with dedicated time to conduct this research.
Employed faculty and or staff with dedicated time to conduct this research.
Students with dedicated time as part of their training to conduct this research.
Volunteers
Other

23.2. Describe the staff and justify their qualifications. Please check-off the items that apply to this study.

All biomedical investigators are privileged and credentialed to perform the study activities in the study locations.
All study staff are trained and credentialed to perform the duties assigned to them.
All study staff have fulfilled the training mandated by their respective departments or institutions.
Other

24. Subject Recruitment and Informed Consent

24.1. Recruitment Tools that will be used by the local site (check a box only if your site will control the use or distribution of the recruitment tool): (check ALL that apply)

Brochures
Clinical Data Warehouse
Email/Electronic Mailing Lists
Flyers
Letters
Newspaper/Magazine Advertisements
Radio/Television Announcements
Subject or Participant Pools
Telephone Scripts
Verbal (Personal Solicitation)
Websites / Social Media Outlets
Other
None of the above

24.1.1. Please specify:
Patients will be recruited from the USC Pain Center via direct physician referrals. Patients who meet diagnostic and other inclusion criteria will be invited to participate.

24.1.2. Describe how you will be obtaining contact information:
Contact information will be obtained from the participant during initial screening and/or from the referring physician.

24.2. Attach copies of all recruitment tools that will be used by the local site. *(Do not attach any advertising or recruitment materials that will not be used at the local site or under control of the local site.)*

Name	Version	Modified
Feasibility Testing Flyer 02-18-2019(0.03)	0.03	3/19/2020 1:34 PM
Usability Testing Flyer 02-18-2019(0.03)	0.03	3/19/2020 1:34 PM

24.3. Informed Consent and Waivers:

**** Please note that child assent and parental permission will be addressed on subsequent pages. Do not complete the following consent questions if adults will not be participating in the study. ****

Check the type(s) of consent or waiver of consent planned for this study: (check ALL that apply)

Written/signed consent (participants will sign an informed consent document)
Alteration of the elements of consent (participants will sign a consent document, but one or more of the basic required elements of consent will be altered or waived)
Waiver of signed informed consent (informed consent document without the signature sections will be provided)
Waiver of consent (participants will not be asked to sign or be given a consent document)

24.7. Attach copies of the informed consent documents(s), information sheets, and any statements of new information/findings or consent addenda (as applicable) that will be used in this study. This set should also contain any assent or parental permission documents that will be used.

Name	Version	Modified
Clinical Trial Informed Consent 09-17-2020 Clean(0.09)	0.09	1/8/2021 2:44 PM
Clinical Trial with change and/or(0.01)	0.01	12/15/2021 12:15 PM
Revised IC to reflect on-line study(0.02)	0.02	9/22/2020 7:33 AM
User Testing Informed Consent 02-18-2020 Clean(0.08)	0.08	1/8/2021 2:44 PM

Click here to obtain an IRB Informed Consent Template and instructions for preparing the consent form.
Consent forms submitted to the IRB should comply with these instructions.

**A qualified interpreter is an individual who is fluent (can speak, read and write) in English and the language of the subject, and (preferably) understands human research informed consent requirements.The interpreter should not be a member of the potential subject's family. Although it may be necessary in some rare cases to have a bilingual family member or staff person serve as a medical interpreter, keep in mind the following issues.*

1. The routine use of ad hoc interpreters should be avoided.
2. Children should not be asked to serve as an interpreter.
3. Complex ideas and treatment regimens may demand that a trained professional be employed.
4. Issues of privacy must be considered if family members are asked to translate.

Personnel from section 2.1 obtaining consent/permission/assent:

Last Name	First Name	Organization	Study Role	Certifications	Obtain Consent
Zhang	Yao-Ping	ANESTHESIOLOGY	Research Coordinator		yes

If the above list is incomplete or incorrect, please navigate to item 2.1 and make your changes there.

24.8. Describe the circumstances and location of the process of informed consent: (check ALL that apply)

In a private area

In a waiting room, open ward, group, or public setting

Online, over the telephone, by mail, or via fax

Other

** NOTE: When participants sign the informed consent electronically, a copy of the informed consent document must be provided to them.

24.8.1. If Other, please specify:
USC Redcap platform for consenting online

24.9. Describe how you will assess the individual's comprehension of the research and what it means to participate, including understanding of the voluntary nature of participating. (check ALL that apply)

An assessment tool will be used. (attach a copy of the tool below)

This will be verbally assessed. Individuals will be asked to answer the following questions (as applicable): (1) What are you being asked to do? (2) What question is this study trying to answer? (3) What are the potential risks of participating in this study? (4) How often will you need to come in for study visits? (5) What is the difference between participating in this study and your standard medical care? (6) What should you do if you decide to withdraw from the study?

Other (specify below)

24.10. Describe all measures that will be taken during the recruitment and consent process to ensure that individuals have adequate time to consider participation and to safeguard against potential coercion and undue influence: (check ALL that apply)

The informed consent process will begin with a concise and focused presentation of the key information that is most likely to assist a prospective participant in understanding the reasons why one might or might not want to participate in the research

They will not be forced, threatened or coerced in any way to participate in this research, and no undue influence or other form of constraint will be used to recruit individuals to participate in this research or to retain currently enrolled subjects. (Note: "Coercion" is the use or threat of the use of force to gain compliance. "Undue influence" is when an individual who is in a position of authority (e.g., physician, teacher, employer) exerts inappropriate or excessive manipulation to gain power and compliance over a vulnerable individual (potential research subject). "Constraint" means force, obligation, or pressure.)

They will not be punished or denied something which they would normally receive (e.g., threatening to withdraw health services to which an individual would otherwise be entitled) if they choose not to participate in this research or choose to withdraw early from participation.

They will be given an adequate amount of time to consider participation in the study relative to the initiation of study procedures.

The information presented to individuals during recruitment and consent will reflect that provided in the informed consent document/informed consent script.

The recruitment and consent process will not promise them a certainty of cure or benefit beyond what is outlined in the informed consent document/informed consent script.

The recruitment and consent process will take place in an area in which it is possible to maintain privacy and confidentiality.

They will be given the opportunity to take the informed consent document home in order to discuss participation with their family, friends and/or others before making a definitive decision.

They will receive payment for their participation, but the amount of payment will be commensurate with their participation (not an inducement for participation), and receipt of the payment will not be contingent upon the individual's completion of the study. (Note: The specific method, schedule, and amount of payment must be outlined in the payment section of the application.)

Other (explain below)

25. Financial Obligation and Compensation

25.1. Financial Obligation: Choose the response that best describes the cost to participants.

All costs are covered by the sponsor or funder.

Research costs are paid by the sponsor or funding agency; routine health care costs are the responsibility of the participants and/or their healthcare plans.

All costs are the responsibility of the participants and/or their healthcare plans.

Drug trials sponsored by the National Cancer Institute or other national institutes.

There are no costs related to participation.

Other

25.1.A. Consent Text: The following financial obligation statement must be contained in the informed consents for this study: (edit only as necessary. If your study has a contract, this language must be consistent with the contract language)
Some tests and procedures are done only because of the research. The study will pay for tests and procedures that are done only because you are in this study.

Some tests and procedures are done for your routine health care, and you would receive them even if you were not participating in this study. You and/or your health plan/insurance will be billed for the tests and

procedures you need for routine health care while you are in this study. You will be billed in the same way as if you were not in a study. You will be responsible for any co-payments and deductibles required by your insurance. Some health plans/insurance companies will not pay these costs for people taking part in studies. Check with your health plan/insurance company to find out what they will pay for. If you have any questions about which tests or procedures will be billed to you and/or your health plan/insurance, ask the study doctor.

When a drug/device is provided by the sponsor, add:

The study drug/device will be provided by the sponsor free of charge while you are participating in this study.

When a drug/device is not provided by the sponsor, add:

You and/or your health plan/insurance will have to pay for the study device/drug.

25.2. Payment for Participation: Describe how much, if any, financial or other form of compensation will be provided to the subject/family. Describe the requisite conditions that must be fulfilled to receive full or partial compensation. Describe the proposed method of timing and disbursement. If children are involved, please specifically address how the compensation will be distributed to children.
Clinical trial participants will receive reimbursement for their efforts in the study for a total of $70 each ($10 for completion of the initial on-line study sessions, $10 for completion of follow-up study on-line session, and an additional $50 upon return of loaned equipment) via cash or e-card.

Participants in the usability study will receive $40 for participation.

Participants will also be reimbursed for parking and travel expenses if they choose to receive or return equipment to the clinic. Patients will be provided with a pre-paid shipping envelope to return equipment.

26. Participant Privacy and Data Confidentiality

26.1. Privacy Protections: Privacy is a participant's ability to control how other people see, touch, or obtain information about his/her self. Violations of privacy can involve circumstances such as being photographed or videotaped without consent, being asked personal questions in a public setting, being seen without clothing, being observed while conducting personal behavior, or disclosing information about abortions, HIV status, or illegal drug use.

Select the provisions to protect the privacy of the individual during screening, consenting, and conduct of the research: (check ALL that apply)

- **Research procedures will be conducted in person in a private setting.**
- **Data will be captured and reviewed in a private setting.**
- **Only authorized research study personnel will be present during research related activities.**
- **The collection of information about participants is limited to the amount necessary to achieve aims of the research.**
- **Participants will not be approached in a setting or location that may constitute an invasion of privacy or could potentially stigmatize them.**

Other (specify below)

26.1. Please specify:
1 Research procedures done on-line, phone and with HIPAA compliant video-conferencing platform .

26.2. Confidentiality Precautions: Confidentiality is an extension of the concept of privacy; it refers to the participant's understanding of, and agreement to, the ways identifiable information will be collected, stored, and shared. Identifiable information can be printed information, electronic information, or visual information such as photographs.

How will the research data/specimens be labeled? (check ALL that apply)

Data and/or specimens will be directly labeled with personal identifying information. (Identifiable)

Data and/or specimens will be labeled with a code that the research team can link to personal identifying information. (Coded)

Data and/or specimens will not be labeled with any personal identifying information, nor with a code that the research team can link to personal identifying information. (Anonymous)

Other (explain below)

26.3. Study data/specimen will be stored:

Physically

Electronically

Which devices will have study data:

Local computers/laptops

Removable drives (USB, external drives)

Local Server(s)

External Servers (including cloud based services)

Which company/organization will be providing the service?
Amazon Web Services, USC Redcap

Note: Please ensure that the third party's technical infrastructure meets or exceeds the minimum standards set out by ITS.

Please confirm that, at a minimum, the following measures will be taken and enforced:

Electronic data will be stored with appropriate electronic safeguards, such as unique usernames/passwords, and limited to authorized study personnel. Dual factor authentication will be used, if feasible.

Security software (firewall, antivirus, anti-intrusion) will be installed and regularly updated in all servers, workstations, laptops, and other devices used in the study

All computers with access to study data will be scanned regularly (for viruses and spyware, etc.) and problems will be resolved

Data stored on a removable drive will be encrypted and have proper access controls

Data transfer will be encrypted

26.4. Will identified data and/or specimens be sent outside the institution to a third party (such as a study sponsor, federal agency, or another institution)?
Yes **No**

26.5. What will happen to the research data and/or specimens at the conclusion of the study? (check ALL that apply)

Direct identifiers and/or the key to the codes will be destroyed upon completion of the research (all data/specimens will be stripped of identifying information and/or the key to codes destroyed, paper documents shredded, electronic files purged, electronic media securely erased)

Retained for study record keeping purposes per institutional policy

Retained by the investigator for future research use

Retained for future research use (submit data or tissue to an existing repository/bank)

Restricted use data will be destroyed or returned to the source

No direct or indirect identifiers are being collected. The anonymous data and/or specimens will be retained at the discretion of the investigator

This research is a clinical trial conducted under FDA regulations. Direct identifiers and/or the key to the codes will be destroyed as directed by the sponsor (IND/IDE holder) in accordance with FDA regulations

The NIH requires that the records be retained for three years following the completion of the study

Other (specify below)

26.6. Do you have, or plan to apply for, a Certificate of Confidentiality for this study?
Yes No

NOTE: NIH-funded research in which identifiable, sensitive information is used, including research that:

- **Meets the definition of human subjects' research, including exempt research in which subjects can be identified**
- **Is collecting or using human bio specimens that are identifiable or that have a risk of being identifiable**
- **Involves the generation of individual level human genomic data**
- **Involves any other information that might identify a person**

is automatically protected by a certificate of confidentiality from the NIH.
Instructions on how to obtain a Certificate of Confidentiality are available at the National Institutes of Health Certificate of Confidentiality website (http://grants.nih.gov/grants/policy/coc/index.htm) and Chapter 11.4 of the USC Human Subjects Protection Program Policies and Procedures (https://oprs.usc.edu/files/2012/11/Policies-and-Procedures-Jan-2015.pdf). If you have additional questions about procedures for obtaining a Certificate of Confidentiality, contact the USC Office for the Protection of Human Subjects at oprs@usc.edu or at 213-821-1154.

26.6.1 Please attach the Certificate of Confidentiality.

26.6.2 Certificate of Confidentiality Expiration Date:

27. Risk/Benefit Assessment - Risks

27.1. Risks, Discomforts and Potential Harms: Describe the risks associated with each research intervention. Include consideration of physical, psychological, social, and other factors. (check all that apply)

Discrimination based on genetic findings.

Some people may find it upsetting to learn that they have certain mutations or errors in genes that could lead to future health problems for themselves or their children.

Some of the questions may make the participant feel uneasy or embarrassed.

There is a small risk that people who are not connected with this study will learn a participant's identity or their personal information.

The participants are providing highly sensitive, personal information in this study. If people not connected with the study learn this information, they could have problems getting a new job, keeping their current job, finding housing, or getting insurance (health, disability, or life insurance). In highly unlikely situations, they could be charged with a crime.

Biomedical risks, including drug, device, biologics, radiation, surgery or other research procedures (please specify).

The research includes the risk or disclosure that a participant may engage in self-harm or attempt suicide.

Venipuncture risks including: mild discomfort (or pain), bruising and swelling around the puncture site, dizziness or fainting, or infection (rare).

Other (specify below)

27.1.1. Describe the biomedical or other possible risks and discomforts participants could experience during this study: (HSC: *refer to specific sections of the protocol, grant, investigator's brochure or product labeling, if applicable*)
There are minimal risks associated with VR. Some individuals may experience cybersickness or nausea during VR use. Some participants may also find the VR headset uncomfortable. GI may sometimes increase frustration and self-blame if participants do not experience reductions in pain commensurate with guided narration. These risks are considered minimal. Both VR-GI and audio-only GI experiences will be specifically designed to guide patients to reduce their experience of pain rather than fully turn their pain off to reduce this risk. There are minimal risks in the administration of questionnaires and qualitative interviews. Some participants may experience boredom or discomfort during the completion of these procedures. If any participant feels distressed during any research procedure, participation will be immediately terminated at his or her request.

27.2. Describe the precautions that will be taken to minimize risks/harms. (check all that apply)

We will use our best efforts to keep the findings in this study as confidential as possible.

Subjects can choose to skip or stop answering any questions that make them uncomfortable.

Data will be coded and identity stored separate from data.

Data will be collected anonymously.

Biomedical precautions, including precautions relating to drugs, devices, biologics, radiation, surgery or other research procedures (please specify).

Venipuncture by individuals certified and privileged to perform the procedure.

Other (specify below)

27.2.1. Other precautions (including biomedical precautions) that will be taken to minimize risks/harms include: (HSC: *refer to specific sections of the protocol/grant, if applicable*)

To decrease the risk of cybersickness, VR content will be run at the highest possible refresh rate and will be explicitly designed to minimize virtual movement that the user does not have control over, as this can create a disconnect between an individual's visual experience and vestibular system which can increase the likelihood of cybersickness. The prevalence of cybersickness will be evaluated during initial feasibility testing and the VR-GI experiences will be adjusted accordingly, if necessary. VR-GI will be discontinued for any participant who experiences cybersickness. To minimize the discomfort in wearing a VR headset, the duration of time participants spend in VR will be limited to ~15 minutes at a time. Participants may discontinue the intervention if they find the headset uncomfortable.

Headsets will be cleaned and sanitized before being given to the patients.

To minimize the psychological risk of frustration or self-blame due to participants not experiencing reductions in their experience of pain, this possibility will be explicitly addressed during the consenting process. It will be emphasized that changes in the experience of pain will likely happen gradually, rather than all at once. Additionally, participants will be guided during the VR-GI experiences to reduce their pain intensity, rather than turn off their pain entirely to appropriately set participants' expectations and to minimize the risk of frustration or self-blame. The extent of pain reduction visualized in VR-GI may be increased at the discretion of the participant throughout the intervention. Participants will be able to contact Dr. Richeimer or Dr. Weinstein during the intervention if they experience frustration or self-blame.

28. Risk/Benefit Analysis - Potential Benefits and Alternatives

28.1. Describe any potential for direct benefits to participants in the study: (check all that apply)

There are no direct benefits to research participants

Improvement in some or all of participants' symptoms

Improvement in some or all of participants' survival or longevity

Information gained from testing or monitoring procedures

Provision of drug or device

Reduced side effects

Other (explain below)

28.2. Describe potential benefits to society, if any. (check all that apply)

The advancement of knowledge

A new treatment or therapy for the condition under study

None

Other (explain below)

28.3. What are the alternatives to participation? (check all that apply)

Not participating

Continue current medical care for their condition

Participation in other research studies

Palliative care

No treatment or therapy

Participate in other subject pool activities

Other (specify below)

28.4. Risks in relation to benefits:

The potential benefits to the research participants justify exposure of the participants to the risks.

The potential benefits to humanity justify exposure of the participants to the risks.

Other (specify below)

35. Is the HIPAA Privacy Rule Applicable?

35.1. Do you intend to access, review, collect, use, or disclose Protected Health Information (PHI/ePHI) which includes either patient and/or participant data, in your research? Answer yes if you intend to do any of the following:

- Look at medical records (paper or electronic) to identify potential research participants
- Look at clinic logs to identify potential research participants
- Record demographic information obtained from medical records (paper or electronic)
- Record health information obtained from medical records (paper or electronic)
- Obtain information from laboratory reports, pathology reports, radiology reports or images, or other reports from medical or mental health testing and treatment
- Obtain information from medical billing records
- Record or use medical record numbers or other information that could be used to identify an individual (review the list of HIPAA identifiers below)
    - Name/Initials
    - Street address, city*, county*, precinct*, zip code*, or equivalent geocodes*
    - All elements of dates (except year) directly related to an individual (date of birth, admission date, discharge date, date of death)*
    - Elements of date, including year, for persons 90 or older

- Telephone number
- Fax number
- Electronic mail address
- Social Security Number
- Medical record number
- Health plan identification number
- Account number
- Certificate/license number
- Vehicle identifiers and serial numbers, including license plate number
- Device identifiers and serial number
- Web addresses (URLs); Internet IP addresses
- Biometric identifiers, including finger and voice print
- Full face photographic images and any comparable images
- Any other unique identifying number, characteristic, or code*

Yes No

35.2. Do you intend to record data that contains any of the 18 elements defined by HIPAA as identifiers (listed above), in your research?
Yes No

35.3. Are you going to record only the personal identifiers marked with an asterisk (*)? If so, you may be able to obtain or use such health information from a healthcare provider for research purposes without an authorization. Under the HIPAA Privacy Rule, this data constitutes a "limited data set". if you are creating or obtaining a limited data set, you must complete a Data Use Agreement. Attach a copy of the signed Data Use Agreement below.

Name	Version	Modified

There are no items to display

35.4. Will you be recording HIV data?
Yes **No**

35.5. Will you be collecting or accessing mental health records from a mental health practitioner?
Yes **No**

35.6. Will you be collecting or accessing substance abuse treatment records?
Yes **No**

USC Template Data Use Agreement
** If your Data Use Agreement does not use USC's template form, please contact USC's Office of Compliance at complian@usc.edu or 213-740-8258 to submit the Data Use Agreement for further review and approval.

36. HIPAA Analysis

This screen is only required if you indicated HIPAA is applicable by answering "yes" to Question 35.1.

36.1. If you are using or accessing protected health information in order to identify potential participants, indicate if you will be applying for a Partial Waiver of HIPAA Authorization for the purposes of screening and recruiting.

Partial Waiver of HIPAA Authorization for screening, recruiting, and identifying participants
None of the Above

36.2. If you are using or accessing protected health information to conduct the research, please select whether you will be obtaining authorization from the participant or requesting a Full Waiver of HIPAA Authorization.

Obtaining HIPAA authorization from participant
Full Waiver of HIPAA Authorization
Both

Click here **to download the "Instructions for Completing HIPAA Research Authorization Form" and the HIPAA research authorization forms approved by the USC Office of Compliance (scroll down to "Research (300))".**

36.2.1. Assurance:

I agree to use the current HIPAA research authorization forms and make only those changes described in the ﷺInstructions for Completing HIPAA Authorization Form.ﷺ
I modified the HIPAA research authorization form and received approval from the USC Office of Compliance to use the modified form.

38. Partial Waiver of HIPAA Authorization

This screen is required only if HIPAA is applicable and you indicated you are requesting a Partial Waiver of HIPAA Authorization (Question 36.1.)

If you are applying for a partial waiver of authorization for the purposes of screening, recruitment, and subject identification, provide justification per 45 CFR 164.

38.1. How will you protect PHI/ePHI (Protected Health Information) from improper use and disclosure? (check all that apply)

PHI/ePHI will be used only for the purposes of assessing eligibility and identifying potential participants.
All source and research documents containing PHI/ePHI will be stored and maintained in a locked/password protected area accessible only to study staff.
Study data will be coded or de-identified prior to being sent outside the study team.
Other

38.2. How will you destroy identifiers at the earliest opportunity consistent with the conduct of the research? (check all that apply)

No identifiers or links to identifiers will be recorded during the data collection process.
Direct or Coded Identifiers will be maintained only until the study is completed. After that, the identifiers will be shredded and electronic records purged.

The link between study participants and study ID numbers will be destroyed (shredded/purged) when study activities are complete.

Other

38.2.1. Describe the plan to destroy identifiers at the earliest opportunity consistent with conduct of the research. If there is a health or research justification for retaining the identifiers, or if such retention is required by law, please explain.
Records will be retained according to NIH and FDA regulations.

38.3. By checking the "I Agree" box you are providing assurance that PHI/ePHI will not be reused or disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI/ePHI is permitted by the Privacy Rule.

I Agree

38.4. The research could not practicably be conducted without the requested waiver or alteration because: (check all that apply)

PHI/ePHI is required to identify potential participants who meet the eligibility criteria.

Other

38.5. The research could not practicably be conducted without access to and use of the PHI/ePHI because: (check all that apply)

PHI/ePHI is required to identify potential participants who meet the eligibility criteria.

During the recruitment process, PHI/ePHI is needed in order to contact potential participants.

Other

38.6. By checking the "I Agree" box you are providing assurance that PHI/ePHI requested will be the minimum amount necessary to conduct the research or meet the research objectives.

I Agree

39. Conflict of Interest Information

39.1. Instructions: Click on the name of each study team member and indicate whether they have a potential financial conflict of interest related to this study. If they have a conflict of interest, click on the conflict that has been reported in diSClose. If the conflict is not listed, ask the study team member to update their disclosure information in diSClose before completing this section.

Study Staff	Role	COI Annual Disclosure Status	Conflicts
Steven Richeimer	Principal Investigator	Current: due on 7/14/2023	No conflicts identified
Faye Weinstein	Co-Investigator	Current: due on 7/14/2023	No conflicts identified
Doerte Junghaenel	Data Analyst/Statistician	Current: due on 7/27/2023	No conflicts identified

Iris Yao	Data Analyst/Statistician	No disclosure on file	No conflicts identified
Yao-Ping Zhang	Research Coordinator	No disclosure on file	No conflicts identified

40. Additional Supporting Documents

40.1. Attach any other documents that have not been specifically requested in previous questions, but are needed for IRB review.

Name	Version	Modified
VRGI-USC Trial - Slides_ Onboarding irb.pptx(0.01)	0.01	2/19/2021 1:45 PM
VRGI-USC Trial - Slides_ Recruitment Consent irb.pptx(0.01)	0.01	2/19/2021 1:45 PM

40.2. If there is any additional information that you wish to communicate about the application include it below. Please note, this section should not be used instead of the standard application items.

50. Required Approvals (Post-Submission)

This screen indicates the approvals received once the proposal has been submitted.

50.1. Pending Division/Department Approvals:

Name	Division/Department	Parent Campus

There are no items to display

50.2. Received Division/Department Approvals:

Name	Division/Department	Parent Campus
ANESTHESIOLOGY	Department	USC-Health Sciences (HSC)

50a.2. Select any additional department or division approvals that may be needed for this study. When the conduct of research involves services not under the control of the investigator (such as radiology, pathology, or nursing) those departments should be added here. Do not specify departments or divisions already listed above. If the service or department does not presently have electronic review, attach a written approval or agreement to 50a.3.

Name	Division/Department	Campus

There are no items to display

50a.3. Are there other campus committees, services or departments that need to review and approve this protocol? If so list the name(s) of the committee(s) and attach approval memos as applicable.

Committee Name	Committee Chair	Approval Memo
There are no items to display		

50a.4. Will the research be conducted through the CTU**?**
Yes **No**

99. Instructions for Submission

You have reached the end of the application. When you are sure of the content, the following steps may be taken to submit your application for review.

1. Click the **"Finish"** button on the top or bottom application navigator bar to return to the workspace.
2. Use the **Hide/Show Errors** above to determine that all sections of the application are filled out correctly.
3. Use the **"Send Study Ready Notification"** activity to send an email to the Principal Investigator and Co-Investigators with instructions for reviewing and submitting the application.
4. **All listed Co-Investigators (indicated in item 2.1.) must use the "Agree to Participate" activity and answer yes.**
5. Once all the Co-Investigators have agreed to participate, the **Principal Investigator** (indicated in item 2.1.) can submit the application by using the **"Submit Application to ____"**, where ____ indicates the IRB you are submitting to.
6. The PI will have to check the PI endorsement box. The PI will also have to check the student endorsement box if it is applicable.
7. The application is submitted. The state indicator in the top left of the workspace will no longer display Pre Submission.
8. The PI and Study Contact Person will receive an email confirming the application has been submitted.

4.4. Funding Source

Please enter the fields below and click 'OK' when done.

4.4.1. *If you cannot find the entity in the list above, click here:*

* **Write-In Entity:**
National Center for Medical Rehabilitation Research at the Eunice Kennedy Shriver National Institute of Child Health & Human Development and the Center for Translation of Rehabilitation Engineering Advances and Technology

4.4.2. * **Named Principal Investigator:**
Richard Greenwald

4.4.3. Institution awarded the grant-award:
NICHD

4.4.4. Grant-award number provided by the Sponsor:
P2CHD086841

4.4.5. Title of the Funding Project, if applicable:
Virtual Reality Guided Imagery Intervention for Chronic Pain

4.4.6. * **Type of Funding:**
Federal: Center Grant *

4.4.7. **Attach a copy of the proposal/contract/grant with the project budget. Copies of the documents submitted to the funding agency, including the budget detail, should be submitted.** (salary information need not be displayed or included.)

Name	Version	Modified
1572 Limbix Assistance Plan 02212019 (1).pdf(0.01)	0.01	7/2/2019 12:02 PM

4.4. Funding Source

Please enter the fields below and click 'OK' when done.

4.4.1. *If you cannot find the entity in the list above, click here:*

* **Write-In Entity:**
National Institutes of Health

4.4.2. * **Named Principal Investigator:**
Benjamin Lewis & Steven Richeimer

4.4.3. **Institution awarded the grant-award:**
Limbix Health Inc.

4.4.4. **Grant-award number provided by the Sponsor:**
R43 DA049617

4.4.5. **Title of the Funding Project, if applicable:**
At-Home Virtual Reality Guided Imagery Intervention for Chronic Pain

4.4.6. * **Type of Funding:**
Federal: Grant *

4.4.7. **Attach a copy of the proposal/contract/grant with the project budget. Copies of the documents submitted to the funding agency, including the budget detail, should be submitted.** (salary information need not be displayed or included.)

Name	Version	Modified
Grant(0.01)	0.01	7/15/2019 5:09 PM

18.1 Device Entry

Please enter the fields below and click 'OK' when done.

18.1.1. * **Indicate the generic and brand names of the device.**
Limbix Virtual Reality Guided Imagery

18.1.2. Attach the requisition form for this device.

18.1.3. * **Indicate the category of regulation for this device:**

The device is exempt from IDE regulations
The device has a humanitarian device exemption - HDE
The device qualifies for an abbreviated IDE - nonsignificant risk device
The device requires an IDE - significant risk device

18.1.6. If the device qualifies for an *abbreviated IDE (nonsignificant risk devices)*, the following must be true:

The device is not a banned device
The sponsor will comply with FDA requirements for monitoring the investigation (21 CFR 812.46).
The investigator sponsor/investigator will comply with FDA requirements for records and reports (21 CFR 812.140, 21 CFR 812.150).
The investigator will not market or promote this device (21 CFR 812.7).
The sponsor ensures that each investigator participating in an investigation of the device obtains consent (21 CFR 50) from each subject under the investigator's care and documents it, unless documentation is waived.
The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval

You must also attach documentation at 18.1.6.1 indicating that the device poses a nonsignificant risk (NSR) of harm to the study subjects from the sponsor with an explanation of its NSR determination and any other information that may assist the IRB in evaluating the risk of the study including:

- The sponsor should provide the IRB with a description of the device,
- reports of prior investigations with the device,
- the proposed investigational plan,
- a description of patient selection criteria and monitoring procedures,
- as well as any other information that the IRB deems necessary to make its decision.
- The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made.
- The sponsor must inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made.

18.1.6.1. Attach documentation from the sponsor or investigator sponsor supporting the NSR opinion.

Name	Version	Modified
NSR justification(0.01)	0.01	7/15/2019 7:02 PM