Neurofeedback-EEG-VR System for Non-opioid Pain Therapy

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013
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1. PROJECT TITLE

Neurofeedback-EEG-VR (NEVR) System for Non-opioid Pain Therapy

2. PRINCIPAL INVESTIGATOR

Krishnan Chakravarthy, MD, PhD

3. FACILITIES

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La Jolla, CA 92037

4. ESTIMATED DURATION OF THE STUDY

The entire duration of the study will be for 12 months.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

This project will investigate an innovative, non-invasive, non-pharmacological pain treatment concept. There is evidence that Virtual Reality usage can assist with acute pain management. In addition, there is evidence that EEG-based neurofeedback (NF), which is training people to control their brainwaves, has the ability to reduce chronic pain perception. Therefore, we will investigate whether a system combining these two methodologies has the potential to assist with both acute and chronic pain management. We call this system Nf +Eeg+VR=NEVR.

6. SPECIFIC AIMS

Aim 1: Validate NEVR on patients with FBSS: 20 chronic back pain patients will be recruited at UCSD and undergo 20 sessions of NF training with the NEVR prototype. Their pain impact will be assessed through an extensive cognitive and functional battery before and after the first and last NF sessions, along with feedback surveys.

Aim 2: Define the system specifications and design the Phase II system: QUASAR will analyze the collected EEG data to determine the minimal subset of electrodes that would be necessary to reliably measure alpha activity in this population. QUASAR will then review the user feedback and develop system specifications and a concept design for a new headset to be built under Phase II.

7. BACKGROUND AND SIGNIFICANCE

Pain is one of the most common and debilitating symptoms of a wide range of injuries and diseases. Its treatment often relies on prescription or over-the-counter pharmaceutical medications such as Nonsteroidal anti-inflammatory drugs (NSAIDs), Acetaminophen, corticosteroids, antidepressants, anticonvulsants, and opioids. There are also non-pharmacological pain management methods such as transcutaneous electrical nerve stimulation (TENS), physical therapy, as well as alternative approaches including thermal, acupuncture, and meditation. Physicians typically iteratively explore these options as they strive to identify the most suitable methods for each patient. Unfortunately, one of the most commonly prescribed pain treatments, opioids, has a potential to lead to addiction, which has led to an epidemic of opioid over-prescription and abuse, with dangerous personal and societal consequences. This opioid crisis is a principal issue in public health with over 47,000 related annual deaths, as well as social and economic welfare costs of over $78.5 billion a year in the USA. Safe and effective alternatives for treating pain that reduce dependence on opioids are, therefore, urgently needed to address this emergency.

Proposed Solution: This project proposes a non-invasive, non-pharmacological alternative that could treat pain

by combining an innovative electroencephalography (EEG)-based Neurofeedback (NF) solution in an immersive virtual reality (VR) environment. This combined NF-EEG-VR (NEVR) pain treatment system is designed to specifically address the underlying brain activity associated with perception of (or attention to) pain. In the scope of this project, we will initially focus our work on chronic low back pain (cLBP) as this is a growing segment of chronic pain sufferers with a 39% worldwide lifetime prevalence, and whose sufferers have historically been a heavy user population of opiates. In the Phase I SBIR study, NEVR will be validated on patients with chronic lower back pain of multifactorial etiology.

8. PROGRESS REPORT

None. This is a new study.

9. RESEARCH DESIGN AND METHODS

This will be a single arm clinical trial with up to 25 subjects undergoing NF training in VR using the NEVR prototype and protocol. This is a feasibility study where only one arm (NF group) is needed for demonstration of feasibility; the number of subjects is based on a recently published study by Mayaud et al. 2019.

Each patient will be recruited from Dr. Chakravarthy's patient population, and after signing informed consent will undergo a cognitive and behavioral pain assessment followed by 20 NF sessions, every other day or 3 times per week. Each session will take up to 1 hour and will consist of: donning of NEVR system, recording EEG while subjects sit with their Eyes Open then Eyes Closed for EEG threshold calibration, followed by performing six 5-minute blocks of NF. Subjects will then be asked to conduct a brief usability survey after each session. At the end of the 20 sessions, subjects will undergo the same cognitive and behavioral assessment conducted at the study's onset.

The NEVR device:

The device to be used in this protocol (NEVR) is an integration of 3 components: 1) QUASAR's 24 channel dry EEG headset (DSI-24), 2) the HTC Vive, and 3) an alpha -activity-based NF protocol. (Figure 1) The DSI-24 is a dry electrode EEG headset that is sold commercially as a research device, while the HTC Vive VR headset is sold commercially as a consumer device. Integration of both hardware devices will include the addition of harnesses to improve comfort and distribution of weight while wearing both devices.

Electrical Safety: Safety considerations for the dry electrode EEG sensors and DSI-24 headset have been addressed by testing and certifying the device according to the Electromagnetic Compatibility Directive (EMC) testing according to ETSI EN 301 489-1 (2011/09) V1.9.2 and ETSI EN 301 489-17 (2012/09) V2.2.1; the Low Voltage Directive (LVD) testing according to EN 61010-1:201. During the set-up of the headset, contact between the electrodes and the skin is assessed via a measurement of the contact impedance. To accomplish this, a very small current is applied to the skin. According to the ANSI/AAMI EC38:1998 safety standard, which is the applicable medical standard, the direct current through the patient-electrode connection should not exceed 0.1 µA. Our system exposes subjects to a current of 0.0012 µA, far below this safety threshold. For comparison, holding a 1.5V AAA battery would result in a current of 0.75 µA, or 700 times that of our system.

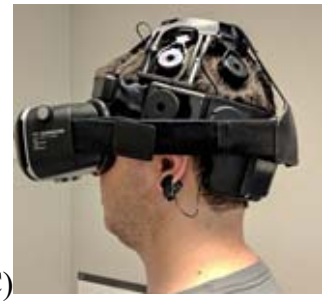
A)  B)  C) 

Figure 1. NEVR Hardware components: A) QUASAR DSI-24 EEG headset; B) HTC Vive Virtual Reality (VR) headset; C), DSI-24 headset work with a VR headset.

NF Protocol:
During each session, subjects will sit in a comfortable seat, and the experimenter will place the headset, which requires no skin abrasion nor the application of any conductive gels. Set-up time is ~5-15 minutes depending upon the hair type of the participant. Our headsets are designed with mechanical adjustments to fit a wide range of heads (52-62 cm in circumference) and the electrodes are double spring loaded in order to provide comfortable contact against the scalp. Once the headset is placed, the experimenter will work each electrode through the subject's hair to ensure good contact with the scalp, and adequate signal quality as determined by measurement of contact impedance and visual inspection of EEG traces respectively. Once electrode impedances are within the recommended range for the DSI-24 (<1MOhm), and EEG traces show no traces of electrical or motion artifacts, recordings will be initiated.

The first recordings will consist of 2-minute Eyes Open (EO) and Eyes Closed (EC) tests in order to calibrate each individual. Once those recordings are complete, the NF protocol will begin. This protocol involves watching a VR Movie (which the subject can choose from a selection of PG-13 choices). The NF protocol entails extracting alpha activity levels from the EEG signal, setting individual thresholds, and modulating video replay or gaming experience based on the patient ability to increase his or her alpha levels to a target range. When alpha activity falls below the threshold, the video may pause, and/or its brightness/sounds may dim, or a game may progress. Subjects will be given the opportunity to rest between the 5-minute blocks.

Pain Assessments:
Pain assessment will be conducted prior to and after the first, 10th and last sessions via all of the following battery of standardized subjective, objective, behavioral and functional evaluation tests:
2) Numerical Rating Scale (NRS, or Visual Analog Pain Score (VAS);
Pain scores are measured using a visual analog scale. This consists of a 10 cm line with "no pain" written at one end and the "worst imaginable pain" written at the other end. The patient is asked to place a mark along the line that corresponds with their pain. The distance, in cm, from the no pain end to the location of the mark gives a measurement of the pain. Subjects will be asked to rate their spontaneous pain and evoked pain to movement.
4) The DALLAS scale;37
A self-reported disability scale for patients with low back pain assessing the impact on everyday quality of life: work and leisure, anxiety, depression, and sociability; each subpart varies from zero to one hundred percent.
12) Patient Assessment Global Change; and
The patient assessment global change is a 2-item measure assessing individuals perceived improvement following treatment.

Statistical Analyses:
EEG: QUASAR will analyze the EEG data to track changes in alpha activity over the course of the treatment and correlate those to the clinical outcomes. Change in Alpha activity will be calculated between the first and last EEG recordings after the 20 sessions. Furthermore, QUASAR will review the data to determine the minimal subset of electrode locations that would yield reliable detection of alpha activity needed for this NF protocol.

Behavioral and Cognitive outcomes: QUASAR will conduct statistical analysis of the results of the pain assessments conducted prior to and after treatment with paired t-test or Wilcoxon signed-rank tests to determine the effects of the treatment (both across the first and last sessions and across the entire 20 sessions). In addition, QUASAR will correlate the clinical outcome measures to the EEG results using cross-correlation analyses and Wilcoxon signed-rank test and will account for multiple comparisons according to the methods described in Mayaud et al, 2019.

Questionnaires: Usability survey results will be tabulated and analyzed by QUASAR to inform the design of

the Phase II device.

10. HUMAN SUBJECTS

In order to meet the aims of the study, we will enroll up to 25 subjects that consent and complete all study procedures. Anticipating a standard 10-50% drop-out rate (consented and withdrawn or dropped out), the estimated accrual will be a maximum of 25 total subjects at all sites, depending on screen failures and drop out.

The plan is to recruit subjects UCSD, with a maximum enrollment of 25 subjects.

Subject selection:
Approval from the UCSD IRB will be obtained prior to study enrollment. Informed, written consent will be obtained from ALL subjects who agree to participate. We expect representation of minorities since we will recruit the subjects from the San Diego area, which has good representation from Hispanic, Asian and African American communities. There will not be any exclusion based on race or ethnicity.

Inclusion/exclusion criteria:
Inclusion Criteria

- Must present with chronic back pain that can be of multifactorial etiology inclusive of axial and radicular back pain
- 18 years of age or older
- Report a Numerical Rating Scale (NRS, or Visual Analog Score VAS) score of greater than 6/10
- Must be willing to for the duration of the study make no pharmacological adjustments or have additional Interventional therapies, as reported by the patient
- Must have the cognitive capacity to provide consent/assent
- Must be able to sit up in a chair during the recording session
- Must demonstrate understanding of the protocol, its purpose and subject participation
- Headsize >54cm and <62cm in circumference in order to fit the current headset design
- Must be fluent in English

Exclusion Criteria:

- Measured head size too small or too large for the EEG equipment
- Any significant skull defect
- History of a recent craniotomy (within the last six months)
- Any signs of scalp inflammation, irritation, or abnormal skin conditions
- History of epilepsy or seizures
- Known allergies to any material to be used in this project
- Sight disabilities that make participation impractical
- Hair styles with thick braids (e.g. dread locks, braids thicker than 0.5")

Due to the nature of the VR program, we cannot include subjects who cannot speak English. The program uses English instructions that is only accessible to subjects who have the headset on. As a result, we cannot use translators for this research study.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Patients will be recruited from UCSD Pain Clinic's current patient population. The PI and Sub-investigators (listed below) will refer subjects to the study who are interested in participating in the study. The investigators associated with this study will inform the UCSD Pain Clinic physicians at one of their weekly clinic in-service meetings of this study and its eligibility requirements once this study is IRB approved. Recruitment will not be limited to the UCSD. Outside referrals will be accepted from community physicians. Subjects' participation or non-participation will in no way affect their current or future medical care.

Interested patients will be referred to Krishnan Chakravarthy, MD, PhD or Katie Lam at UCSD to be scheduled

for study visit #1, at which time the subject will be consented.

If we receive no referrals as a result of this recruitment strategy and the need for additional recruitment materials/avenues are needed, the study flyer, poster, postcards, and emails to community doctors will be submitted at a later date for review and approval by UCSD IRB prior to use.

Recruitment materials will be reviewed and approved by the IRB before they are used for the study.

For pre-screening recruitment purposes ONLY, we are requesting for a partial waiver of informed consent to interrogate the EPIC database and identify potential prospective research participants who meet the eligibility criteria for enrollment as listed in Item 10 Human Subjects.

The investigator believes the pre-screening to be used for recruitment meets the following requirements for this request per 46 CFR 46.116:

1. The (pre-screening) procedure is considered no more than minimal risk to the potential subjects, since we will not perform any procedure and the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life.
2. The waiver or alternation will not adversely affect the rights and welfare of the subjects.
3. The (pre-screening) research could not practicably be carried out without the waiver or alternation; and.
4. Once the potential participants are identified, we will contact their PCP and ask them to distribute one of our IRB-approved flyers. If interested, study participants will contact the study team and schedule a screening visit (per IRB-approved study protocol). Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Recruitment procedures will also involve the review of subject records by designated study personnel (e.g., investigators and/or study coordinators) in order to identify potentially eligible subjects. Since Protected Health Information (PHI) will be accessed via the hospital's medical record database prior to contacting the potential subject about the research study, we are requesting a partial waiver of HIPAA authorization for access to PHI for purposes of prescreening only.

Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent.

A brief subset of preliminary eligibility criteria such as age, gender, and pain diagnosis in the past 12 months, will be reviewed by study personnel to determine subjects' preliminary eligibility for the research study. No written record of this information will be created. There will be no direct contact of the potential research subject by the pre-screener (i.e., study staff). The pre-screener will ask the subject's treating physician to approach the subject. The treating physician will further discuss the research study with the potential subject and ask whether they would like to be contacted by study staff to discuss the trial (i.e., counseling) and/or provide the potential subject with the study staff's contact information. Eligibility may be formally determined at the time of counseling, but any research-specific screening procedures will only be performed after informed consent is obtained and a standard, stand-alone HIPAA authorization form is signed.

For the partial waiver of individual authorization for pre-screening recruitment purposes ONLY of individual HIPPA/Protected Health Information. The following conditions apply:

1. The (pre-screening) research involves no more than minimal risk, since we will not perform any procedure and the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life.

2. Granting of waiver for recruitment purposes only will not adversely affect privacy rights and welfare of the individuals whose records will be used.
3. The pre-screening could not practicably be conducted without a waiver.
4. The pre-screening could not practicably be conducted without use of PHI.
5. The privacy risks are reasonable relative to the anticipated benefits of research.
6. An adequate plan to protect identifiers from improper use and disclosure is included in Item 16.
7. Participant identifiers/sensitive information shall be removed and/or destroyed as soon as they are no longer needed and in accordance with UCSD policy. The investigators have procedures in place to periodically review collected participant identifiers/sensitive information to ensure it is still required to satisfy a particular purpose or carry out a function.
8. The participants' PHI will not be re-used or disclosed for other purposes.

Once the potential participants are identified, we will contact their PCP and ask them to distribute one of our IRB-approved flyers. If interested, study participants will contact the study team and schedule a screening visit (per IRB-approved study protocol). Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

We will not be recruiting armed services personnel.

12. INFORMED CONSENT

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the UCSD Institutional Review Board responsible for oversight of the study. Written informed consent will be obtained from the subject from a member of the study staff who has appropriate training and sufficient knowledge of the study. At the time potential subjects contact us regarding the study, any questions they may have will be answered by a member of the study staff. If the potential subject is still interested in participating, a clinic visit will be scheduled. The subject will be informed of the time that needs to be allotted for their first visit in which the informed consent will be administered.

Informed consent will be obtained in a private clinic room. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks, and benefits of participation. This information will be explained to the study subject in a face-to-face setting by the individual consent the subject. Subjects will be encouraged to ask questions throughout the consent process and encouraged to discuss their participation with trusted advisors, such as family members, close friends, etc. Subjects will be allotted sufficient time to consider whether or not to participate in the research study. After allowing the potential subject time to read the informed consent the study staff and/or investigator will answer and address any questions or concerns the subject may have. Once all questions and concerns have been addressed and the subject wishes to participate, they will be asked to sign the informed consent.

Individuals unable to speak English will not be excluded from participating in this study. The approved informed consent and any subsequent versions will be translated into Spanish and on a case by case situation any other language that is deemed necessary. The translated informed consent will be submitted to the IRB for approval. The consent process will include a qualified translator in the subject's native tongue.

Also, during the consent process, the Health Insurance Portability and Accountability Act (HIPAA) Authorization will addressed. A copy of the consent and HIPAA Authorization form as well as the Notice of Privacy Practices booklet will be given to the subject. A copy of the consent will be scanned in the medical record at UCSD.

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13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative is not to participate. Subjects and their pain physician can discuss alternatives such as physical therapy, manual manipulation, regularly prescribed analgesic medications, and standard interventional therapies including steroid injection and radiofrequency ablation. The patient's decision not to participate in the study will not affect their access to standard medical care. Participation is voluntary.

14. POTENTIAL RISKS

Loss of Confidentiality Risk:
Absolute confidentiality cannot be promised because information needs to be shared as described below. However, information will be collected and shared following standards of confidentiality. Subject's identity as a participant in this study will remain strictly confidential. Subjects will be identified in the study under a study-specific code. Should results of this study be published, subjects will not be identified through their name or personal information.

Questionnaires:
Subjects may be uncomfortable answering certain questions. They may also experience boredom, fatigue, or embarrassment.

Privacy: There is no psychological or social risk; all participants will sign an informed consent, have their confidentiality maintained, and be debriefed.

Materials: The device is RoHS compliant and the materials coming in contact with the patients are safe. The electrode tips of the biosensors are coated with Ag/AgCl which is commonly used in FDA-approved EEG and ECG electrodes. The other material that may come in contact with the subjects is the foam padding which is made from a neoprene material commonly used for underwater garments.
Comfort: The DSI-24 headset been designed for comfort and feedback from users indicates high tolerability and comfort in extended continuous wear for periods up to 8 hours. However, should any participant report discomfort from wear of the headset that normal adjustments cannot resolve, the headset will be promptly removed, and the data collection on this subject terminated. Headsets should not be overtightened. On occasion, subjects have reported onset of headaches after wearing a headset too tightly for a prolonged period. In such cases, the headsets are loosened or removed depending on the subject's wishes and/or discomfort level.
Wireless Data Transmission Risk: The primary safety issue of the wireless transmitter is exposure to electromagnetic radiation. The Specific Absorption Rate (SAR) represents the electromagnetic power absorbed in the body. In general, the FCC limits SAR for human exposure to 5 mW/cm2. Exposure to electromagnetic radiation at levels below recommended limits has no known health risk [IEEE, 2006]. The BlueTooth radio in the Wearable Sensing wireless node is a low power device, which is intended for short-range with transmission frequency in the 2.4GHz. Available evidence suggests that there is no clear correlation between low-power wireless use and health issues. Recent studies strongly suggest that the use of cellular telephone equipment does not create health risks [Johansen, 2001, European Commission Directorate, 2002]. Bluetooth technology headsets, which have been popular lately, have transmitter power of less than 1/100 those of electromagnetic cell phones. Most Bluetooth headsets transmit power with specifications: 4 dBm (2.5 mW) at 2.4 GHz. The DSI-24 wireless node will operate at a power range of 0dBm (1 mW) to -10 dBm at 2.4 GHz. For these reasons, the SAR induced by the integrated Bluetooth transmitter meets applicable health and safety standards

VR: The HTC Vive is a commercial consumer device that is believed to be safe, though VR usage may pose risks of eyestrain and headache and nausea from the visual experience.

Neurofeedback: Negative side effects from neurofeedback rarely occur, when neurofeedback protocols are

well controlled. When present, they have been primarily associated with mild anxiety, fatigue, or frustration during the session itself.

In general, there is a risk that serving as a subject sitting still might make a subject's pain worse. We will try to ensure that subjects are in a comfortable position for the duration of the neurofeedback session, including offering the option of doing the sessions while standing up or laying on the floor. If there is significant concern for intolerability, we will ask the patient to stop the treatment.

Unforeseen Risks:
It is possible for any study to cause unwanted side effects. There is also the possibility that there may be unforeseen risks associated with the study which are not yet known. As information becomes available, subjects will be told of any changes in the way the study will be done and of any newly identified risks to which subjects may be exposed that may affect their willingness to continue taking part in this study.

Risk Assessment Summary Statement:

Based on the risk analysis of electrical safety, electrode materials, battery operation of the electronics, headset comfort, wireless transmission risk, QUASAR has assessed its devices to be non-significant risk (NSR) devices.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Dr. Chakravarthy is a pain management specialist and will work with and monitor back pain subjects secondary to FBSS to ensure they inform him of their pain levels. If it appears the protocol is increasing a subject's pain, changes will be made to mitigate it or the testing will be stopped. All subjects will be informed of headache, eye strain and neurofeedback risks and asked to keep the researcher informed of their status. Regular breaks will be scheduled and taken. If despite breaks and resting, subjects continue to experience negative effects, the protocol will be stopped.

QUASAR has addressed risks in its equipment with verifications that its devices meet or exceed relevant safety standards.

Subjects will have the opportunity to drop out of the study at any point. The patient will be informed that the data collected up until the point at which the patient discontinues the study will be analyzed. However, they will be informed that they can withdraw their consent if they do not want their data analyzed. Since being in the study is completely voluntary, a subject can withdraw from the study at any point without any penalties. The study team may follow-up with the subject or asks to do more tests to ensure that they withdraw from the study safely.

Data Safety Monitoring Plan: The PI will monitor study progress and safety. Dr. Chakravarthy will review AEs as they occur and determine their relation to the study.

DSMB: The safety and tolerability of the study medications will also be monitored closely by the protocol team. In addition, a Data Safety Monitoring Board (DSMB) will be convened (after 50% of subjects have completed the study,) to review the project's safety data. At least three experts will comprise the DSMB: a statistician with experience in clinical trials, an expert in HIV clinical trials, and an expert in neurologic HIV disease research. Reports will be prepared by the DSMB and responses will be prepared by the protocol team.

Case report forms (CRF) will be provided for each subject. Subjects must not be identified by name on any study documents. Subjects will be identified by the Patient Identification Number (PID) and Study Identification Number (SID).

All data on the CRF must be legibly recorded in black ink or typed. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction must be initialed and dated by the investigator or a designated, qualified individual. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF as to why the required information was not obtained.

Monitoring: The investigators will review the research records for accuracy, completeness, and legibility. The investigators will also regularly inspect regulatory files to ensure that regulatory requirements are being followed.

The investigator will make study documents (e.g., consent forms, drug distribution forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the Food and Drug Administration (FDA), as required, for confirmation of the study data.

Questionnaires:
If the subject feels uncomfortable, or experiences boredom, fatigue, or embarrassment while responding to the questionnaires, he or she may choose not to answer. Questionnaires will be reviewed by a trained psychologist immediately following completion of the measures. If at any time a red flag is identified, the subject will be referred to a trained psychologist for further evaluation and treatment. If the psychologist determines the subject is at imminent risk for self-harm or harm to others during review of the measures, the psychologist will initiate safety protocol. Patient's will be escorted by security to the Emergency Department for further treatment.

Adverse Events:
Safety assessments will include monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs). Subjects will be monitored clinically. The subject will be given the 24-hour number to call for emergencies. The subject will be informed to call at any time for adverse experiences during study participation. This will be recorded in the research notes. The PI will monitor all AEs.

Adverse Event Severity
The investigator will characterize the severity of each AE as mild, moderate or severe. The assessment is subjective and the investigator will use medical judgment to compare the reported AE to similar types of events observed in clinical practice. Guidelines for AE severity assessment are as follows:
• **Mild:** The AE is transient and easily tolerated by the subject.
• **Moderate:** The AE causes the subject discomfort and interrupts the subject's usual activities.
• **Severe:** The AE causes considerable interference with the subject's usual activities; may be incapacitating and may require hospitalization.

Adverse Event Reporting
Any AE that occurs during the subject's participation in the study will be recorded on the AE case report form. Pre-existing medical conditions or symptoms occurring prior to the initiation of the study will not be reported as AEs but a worsening of a pre-existing medical condition or symptom will be reported as an AE. Pain, neurological status and functional impairment should be considered AEs when a subject's complaint for any of these symptoms results in an unscheduled visit and/or when a subject present with new or worsening symptoms as compared to a previous visit. All AEs will be followed until the event is resolved or considered to be stable. If an AE is ongoing when the subject completes the final visit, the AE will be followed until resolution or until 30 days after the last study visit, whichever comes first. Relevant source documentation must be available to confirm the occurrence of an AE and will be provided to the IRB upon request.

The investigator will report the SAE to the reviewing Institutional Review Board (IRB)/Ethics Committee (EC) according to local requirements. Reporting time frames should comply with local or national requirements. In addition, the investigator should report to the sponsor and IRB/EC any device deficiencies that could have led to a SAE, if required by national regulations or by local authorities.

The study staff will ensure that all SAEs and SADEs are reported to IRBs/ECs and competent authorities and/or US FDA as dictated by applicable national regulations.

Confidentiality:
Subjects will be assigned a code number in which all CRFs will be completed. At no time will the subjects' PHI be sent out. All publications and presentations will identify subjects by number only. All records will be stored in a locked filing cabinet in an office only accessible by research staff. Computers used to store subject information are password-protected and only accessible by research staff.

All serious and unexpected adverse events will be reported to the UCSD IRB within 10 working days. Minor protocol violations will be reported to the IRB at continuing reviews. Major protocol violations (such as instances that pose a risk to subjects) will be reported to the IRB within 10 working days. No Data Monitoring Committee has been established for this study.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Patient Confidentiality:
Subjects' identity as a participant in this study will remain strictly confidential. Subjects will be identified in the study under a study-specific code. Identifying information linked to the code will be kept in a separate locked file available only to the study PI and Katie Lam or qualified study staff. This is stored in a locked cabinet in a locked storage room. Should results of this study be published, subjects will not be identified through their name or personal information. All research records will be stored in a locked cabinet at all times. Paper source, electronic source and case report forms will be utilized for the study and will not contain any subject identifiers. If source documents submission is necessary i.e. for SAE reporting, subject will only be identified by their subject number. All correspondence will have the subject's identifiers blank out and replaced with the subject number. All study files are stored in study coordinator's office that is always locked and have limited access only to the study staff.

Security of digital and hard copy data:
All hard copy data obtained will be recorded on designated case report forms with subject number only. Patient identifying information that is linked to subject number will be kept in a locked cabinet in the locked office only accessible by the primary investigator or study coordinator at the Clinical and Translational Research Institute.

Demographic information collected about subjects will be limited to age, sex, ethnicity and hair type (i.e. length and style). This information will not be shared in any way but may be reported in aggregate to characterize the subject population.

De-identified, encrypted electronic data will be stored and transferred over a secure server.

Study visits and recruitment will be conducted in a private clinic room at the KOP pain Clinic, not a public area, hallway or waiting room. Informed consent will be obtained in a private clinic room at ACTRI.

17. POTENTIAL BENEFITS

The potential benefit to the eventual success of this project is providing non-opioid pain alleviation. This would be a large benefit to society in general and patients in particular. The risks to the subjects are mild and even if

they do experience negative effects, those potential effects are transitory. It's possible that subjects might benefit from pain relief during the VR sessions. In addition, subjects may gain some benefit from the neurofeedback portion of the short protocol they are doing. Neurofeedback not only offers benefit to pain sufferers in terms of relief of pain sensation, but has shown potential to assist with anxiety management, emotion calming, and peak performance applications, among others.

18. RISK/BENEFIT RATIO

The risk to benefit ratio is favorable based on the potential benefit of the population as a whole. While individual subjects may not personally experience significant outcomes, the benefit to be gained by the target population outweighs any of the minor risks associated with protocol and its associated procedures.

19. EXPENSE TO PARTICIPANT

Patients will pay $5 for parking. Study procedures will be provided at no cost to the patients.

20. COMPENSATION FOR PARTICIPATION

$200 total for completion of study per subject. $10 for each visit for 20 visits, paid in $30 increments. Payments will be prorated for visits completed if they withdraw from the study.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

All research team members including the primary investigator, sub-investigators, and coordinators have the necessary privileges, certifications, and licenses to perform the duties at the UCSD outlined below.

1. Primary Investigator: Krishnan Chakravarthy, MD, PhD will be responsible for the overall clinical, regulatory, and administrative conduct of the study. Dr. Chakravarthy will recruit subjects, conduct informed consent discussion, perform medical histories and physical assessments, review adverse events for severity, causality, and initiate treatment if necessary, and oversee research staff.

2. Research Coordinator: Katie Lam will assist the PI in screening study patients, providing informed consent, and in doing patient interviews. She will maintain research files, assist with subject recruitment, as noted above, assist with informed consent discussions and document such, perform study procedures, collect data, and report any adverse events after PI review. Additionally, she will assist the PI in maintaining study renewals and other IRB-related tasks.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

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24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

N/A

26. IMPACT ON STAFF

N/A

27. CONFLICT OF INTEREST

N/A

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

N/A

29. OTHER APPROVALS/REGULATED MATERIALS

N/A

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

N/A