Effects of Virtual Reality on Pain and Anxiety Using Validated Survey and Biodata Analyses

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SUMMARY OF CHANGES FROM PREVIOUS VERSION:

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
3.2; 3.3; 3.4; 3.5; 4.0; 5.3	Study inclusion and exclusion criteria were further specified (3.2 and 3.3). Study recruitment process and strategies were further explained and described (3.5). One more study questionnaire was added (4.0). Variables to be collected were described in details (5.3).	Changes were made internally to provide more details about the study particularly about the recruitment process.
3.3; 3.5	Two study exclusion criteria omitted (3.2 and 3.3). New recruitment method added (3.5).	Changes were made internally to include a larger potential cohort and make patient identification easier for study staff and referring providers.

PROTOCOL SUMMARY

- Purpose

  - Examine the feasibility of using Virtual Reality (VR) software VR Solace as a method for treating any-cause chronic pain in hospitalized patients

  - Compare physiological changes during use of VR Solace to patient reported outcomes (PROs).

- Aims

  1) To assess the effects of VR Solace on pain and anxiety as reported by the Numeric Pain Rating Scale (NPRS) and the State-Trait Anxiety Inventory 6 (STAI-6), respectively

    - Measure the subsequent therapeutic response using validated survey data

    - Analysis of demographic characteristics and survey data will be conducted to identify factors associated with greater therapeutic responses to VR Solace in patients with pain

    - Evaluate associations between medical history/lab values to patient PROs

  2) To investigate any correlations between physiological changes during VR Solace use (heart rate, heart rate variability, and pupil diameter) and patient-reported outcomes.

- Demonstrate presence of physiological effects with VR Solace use
- Evaluate which physiological effects are associated with greater therapeutic response

- ❖ Research Procedures
  - Validated survey to assess pain and anxiety pre-VR
  - Administer VR Solace to patients
  - Collect real-time biodata during VR Solace session of 15 minutes
  - Repeat surveys post-VR
  - Data analysis
- ❖ Subject Population
  - Patients currently admitted at Cedars-Sinai Medical Center with chronic pain, independent of admitting diagnosis
- ❖ Duration
  - 1 visit per subject
  - Total study period of 3 months

GENERAL INFORMATION

- ❖ CSMC Co-Investigators
  - All listed on cover page
  - Any other residents to be involved
- ❖ Sponsor/Funder
  - This study is not funded
- ❖ Collaborating Institutions Involved in the Research
  - Not applicable

1.0 BACKGROUND, RATIONALE

Chronic pain is commonly reported in clinical settings, affecting over 20% of the global population.[1] Several studies previously estimated the prevalence of chronic pain to range from 11% to 40% of adults in the United States.[2] Despite significant improvements in medications, procedural interventions, and noninvasive therapies, persistent pain is detrimental to the functional status and psychological well-being of individuals in the community. Furthermore, pain and anxiety have been shown to co-occur in many individuals, and nearly 50% of patients with chronic pain suffer from one or more anxiety disorders.[3] This association is seen across multiple clinical settings and major life domains,[4] and healthcare for its surveillance and treatment is costly and resource-intensive.[5]

Virtual Reality (VR) was first effectively used to treat pain in 1998,[6] and since has become an emerging treatment modality for numerous indications. Its efficacy in treating pain and anxiety

has been demonstrated in acute, surgical or procedural settings,[7, 8] as well as in chronic conditions including cancer.[9] Success of improving mood, stress levels, and pain relief with VR has been repeatedly achieved, and implementation of VR is steadily growing in the field. Despite the increasing use of VR as non-invasive, additive therapy, there are limited studies of VR efficacy exploiting validated survey data from patients in the inpatient setting.[10] Along with patient-reported outcomes, real-time physiological changes have been observed to measure responses to VR use. The physiological changes include gaze tracking, heart rate, skin temperature, respiration rate, blood pressure, and among others.[11] In current literature, very few studies have examined the correlation between real-time physiological changes and patient-reported survey data. In detail, the studies were conducted in limited context such as acute ICU care or use of simple biodata such as oxygen saturation.[12, 13]

Therefore, the purpose of this prospective, observational study is to assess the therapeutic response to VR Solace in patients with chronic pain and anxiety using real-time clinical and survey data. Secondly, with use of relatively more complex biodata, this study can establish a possible association between the patient-reported changes in pain or anxiety levels with several real-time physiological measurements during VR Solace use. This study hopes to pave way not only in developing a standard VR therapy regimen for chronic pain and anxiety, but also in formulating a prediction of an individual's therapeutic response to VR based on biodata and clinical factors.

2.0 STUDY OBJECTIVES

The purpose of this study is to assess the therapeutic response to VR Solace in patients with chronic pain and anxiety using real-time clinical and survey data. Regression analysis of demographic characteristics, lab and survey data will be conducted to better understand the efficacy of VR Solace in treating chronic pain and anxiety. We also aim to explore the possible association between the patient-reported changes in pain or anxiety levels with real-time physiological changes observed during VR Solace use.

3.0 STUDY POPULATION

3.1 SELECTION OF THE STUDY POPULATION

- Will be conducted at one site only, inpatient hospital setting at Cedars-Sinai Medical Center

3.2 INCLUSION CRITERIA

- Age 18+

- Patient-reported or physician-diagnosed (ICD-10 codes) chronic pain defined as: persistent or recurrent pain lasting *longer than 3 months*

- Chronic pain can be classified in 7 subtypes: (1) chronic primary pain, (2) chronic cancer pain, (3) chronic posttraumatic and postsurgical pain, (4) chronic neuropathic

pain, (5) chronic headache and orofacial pain, (6) chronic visceral pain, and (7) chronic musculoskeletal pain.

1. Primary pain: Pain in 1 or more anatomic regions that persists or recurs and is associated with significant emotional distress or significant functional disability and that cannot be better explained by another chronic pain condition.

2. Cancer pain: Pain caused by cancer itself and/or pain from cancer treatment.

3. Posttraumatic and postsurgical pain: Pain after a tissue injury from trauma or surgical procedure

4. Neuropathic pain: Pain and sensory signs along neurodistribution that is anatomically plausible, with previous history of nerve injury at site of lesion

5. Headache and orofacial pain: Pain for at least 50% of the days in the 3-month period.

6. Visceral pain: Pain from the internal organs of head and neck region, and thoracic, abdominal, and pelvic cavities.

7. Musculoskeletal pain: Pain directly from bone, joint, muscle, or related soft tissue

- Endorsing acute pain during admission, within last 24 hours, a measurement of 3 or greater on 11-point scale on validated survey during hospital stay

- Chronic pain does ***not*** need to be primary diagnosis of admission

3.3 EXCLUSION CRITERIA

- No active diagnosis of medical conditions that may cause physiological variations in vital signs (i.e. sepsis, cardiogenic shock/arrhythmia)
- No active diagnosis or undergoing treatment of primary GI cancer

- No active diagnosis of seizures, migraines, severe nausea, severe propensity for motion sickness, or facial/head deformities that would allow for comfortable placement of headset

- Exclusions of patient currently taken a beta blocker in the last 24 hours
- Unable to communicate/read English for survey items
- Unable to use VR independently – patients will be expected to maneuver through questions/steps of the VR system during the session

3.4 SUBJECT SCREENING AND ENROLLMENT

- Data will be prospectively collected during the study period
- Gauge interest from Pain Service Team at Cedars-Sinai Medical Center in collaborating to identify prospective patients

- Primary investigators listed on the cover page will access the records needed for screening
- Medical records will be reviewed for purposes of screening:
  Age – 18+
  Pain Score documented per nursing
  Medications/Treatments – Beta Blockers

3.5 SUBJECT RECRUITMENT

- Subjects will be from both investigators' patients and referrals from other care providers: General medicine wards team, Orthopedics, Gastroenterology inpatient, Pain Medicine team, Supportive Care team (SCM)
- Primary investigators listed on cover page along with other investigators of the project (currently recruiting other investigators) will approach subjects in person
- Patient referrals from other providers at Cedars-Sinai Medical Center
- No advertising will be used
- We will enlist Cedars-Sinai's Enterprise Information Services's (EIS) Honest Enterprise Research Brokers (HERB) Committee to identify inpatients that meet our inclusion criteria.

4.0 STUDY DESIGN AND METHODS

❖ <u>Collection of Survey Data</u>

→ *Primary outcomes*: Evaluate for treatment response in pain/anxiety levels after VR Solace session (1 time)

- Validated pain survey
  - Pain Numeric Rating Scale (pre & post-VR)
- Validated anxiety survey
  - Full or 6-question abridged version of State-Trait Anxiety Inventory (pre & post-VR)

→ *Secondary outcome*: Assess for physiological changes during VR Solace use (heart rate, heart rate variability, and pupil diameter)

- Compare the average physiologic measures (3 listed above) of the first minute with average of last minute of VR use (15 minutes total, not including pre- and post-VR survey time)
- Correlation of the changes in average and survey data/patient-reported outcomes

→ *Covariates*: Consider using these survey variables as covariates in multivariable regression models

- System Usability Scale – subjective assessments of device/system usability
- Simulator sickness questionnaire (SSQ) – Assessing motion sickness + presence survey
- Immersive Tendencies Questionnaire

❖ <u>Collection of Biodata</u>

→ Directly from VR Solace device

- Heart rate, heart rate variability, pupil diameter changes – calculation of averages

- Use as covariates in multivariable regression models

❖ Data Analysis

→ Multivariable linear regression models

- Change in pain/anxiety scores as outcomes – continuous variable
- Covariates of demographic factors, comorbidities, biodata, other survey data (System Usability Scale, Immersive Tendencies Questionnaire)

5.0 DATA COLLECTION AND MANAGEMENT

5.1 DATA PROCUREMENT

- Biodata will be collected by the VR headset during the session.
- Patient-reported outcome data will be collected by surveys administered to the study participants.

5.2 TIME PERIOD OF DATA UNDER REVIEW

- Data under review will be of de-identified data
- Real-time data will be collected at time of VR sessions, which will be held though an estimated time of 6 months. Data will be collected prospectively.
- Information will be kept for an indefinite time.

5.3 VARIABLES COLLECTED

The following data points/variables will be collected:

- Age
- Education
- Gender
- Employment
- Marital status
- Income
- Household size
- Primary admitting diagnosis
- Primary referral diagnosis (provider reported or ICD-10 coded)
- Race
- Ethnicity
- Surgical history (any pain related surgery)
- Social history drug/opiate use)
- Medications/treatments (opioids, MME, start date-end date for at least 3 months)
- Survey data (pre & post-VR session) – described above
- Real-time biodata obtained through VR device – heart rate, heart rate variability, pupil diameter changes

5.4 SOURCE DOCUMENTS

- Only patients' chart/medical records will be used for data collection

5.5 DATA COLLECTION AND STORAGE

- Data will be collected electronically and stored on REDCap/Box
- Only the primary investigators will have access to the data
- Collected information will be de-identified immediately after collection

5.6 CONFIDENTIALITY AND SECURITY OF DATA

- **Secure storage**: Data will be housed in a HIPAA-compliant secure storage system, like REDCap or Box, within the Cedars-Sinai network with access restricted to approved members of the research team.
- **Limited Access:** Private identifiable information, will be accessible only to IRB approved study team members with current IRB training.
- **Unique ID Numbers:** Each patient will be assigned a unique ID number, which will be used to code data and specimens.

6.0 DATA AND SAFETY MONITORING

6.1 DATA AND SAFETY MONITORING PLAN

- Data and Safety Monitoring Plan – There is possibility of adverse events with use of VR such as motion sickness or headaches, in which case the patient will be instructed promptly to remove the headset.
- An investigator will be present at time of VR use, and thorough instructions will be given prior to session
- Data will be collected automatically by device, there will be no subject-investigator interaction to obtain biodata
- Data integrity

  Electronic Research Records

  - All study records will be stored in shared network folder on Cedars-Sinai network (no storage on non-CSMC computer)
  - Access will only be at Cedars-Sinai or through approved VPN access
  - Access will be limited to certified research personnel with IRB approval for access
  - No data will be downloaded to unencrypted portable devices (e.g., flash drive, personal laptop, etc.)

  Linking Lists/Files

  - Linking lists with codes assigned for each subject, will be maintained separately from research data
  - Access to the linking list will be limited to approved research personnel

- Study data will be coded upon abstraction, and any direct identifiers will be maintained separately from data

Identifiable Information

- Study team will destroy identifiable information as soon as possible after it is no longer needed for research purposes
- Identifiable information will not be used or disclosed for any purposes not described in this protocol or the IRB application

Computer Equipment

- All laptops used for collecting and storing research data or patient information will be encrypted in accordance with EIS standards.

- Subject safety - All serious adverse events will be reported to the members of the DSMB and the university IRB within 24 hours. A report of all non-serious adverse events will be provided to the board members and the IRB yearly. NIH will be informed of all actions taken by the IRB as part of the continuing review.
- There are no concerns for any unexpected events, patient harm, or protocol deviations in this study.
- Methods to document data monitoring activity - The study will be monitored by the study investigators who will review the data regularly.

6.2 QUALITY CONTROL AND QUALITY ASSURANCE

- The study investigators will meet at regular intervals to evaluate the protocol and assure adherence to protocol. This will be done after enrollment of the first 10 patients to the protocol. After that the investigators will meet every two months to assess protocol and evaluate data. Additionally, after enrollment of half the patients there will be a meeting of investigators.
- Primary investigators listed on the cover page will all be responsible for the evaluation of data quality which will be assessed after each subject session.

7.0 STATISTICAL CONSIDERATIONS

7.1 STUDY OUTCOME MEASURES

Outcomes will be continuous—change in pain/anxiety levels in response to VR Solace treatment session. The levels will be measured by validated scales, and changes will be calculated based on pre-session and post-session survey responses. Secondary outcomes will also be continuous, as change in averages of first and last minute of the VR Solace session (not including pre- and post-VR survey time).

7.2 SAMPLE SIZE CONSIDERATIONS

- A paired t-test was used to calculate power. The desired power is 80% and 0.05 was used as the significance level.

- To achieve a moderate to large effect of 0.5, we estimate to recruit a sample of 34 patients, and to achieve a larger effect of 0.8, we estimate to recruit a sample of 16 patients.
- No measures to decrease bias/precision such as blinding of staff will be performed, however study protocol will be followed strictly for all subjects in same hospital settings.

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PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1	Revisions 7/14/22	Study PI change	Consistency with other study documents
2	Revisions 7/18/22	Study inclusion and exclusion criteria were further specified (3.2 and 3.3). Study recruitment process and strategies were further explained and described (3.5). One more study questionnaire was added (4.0). Variables to be collected were described in details (5.3).	Changes were made internally to provide more details about the study particularly about the recruitment process.
3	11/16/2022	Two study exclusion criteria omitted (3.2 and 3.3). New recruitment method added (3.5).	Changes were made internally to include a larger potential cohort and make patient identification easier for study staff and referring providers.