Effects of **V**irtual **R**eality on Women Undergoing **B**reast **R**econstruction **VR 4 BR** A Pilot Study

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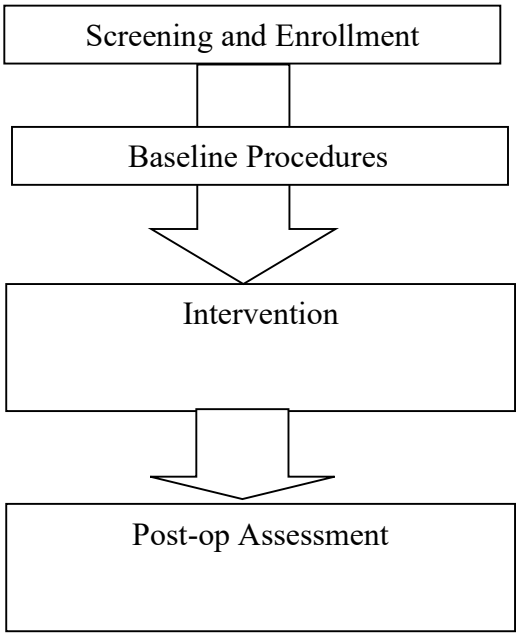
STUDY SCHEMA



Primary endpoint: Opioid use

BACKGROUND AND RATIONALE

1.1 Disease Background

Pain management is a crucial aspect of study participant-centered care. However, the current increase in prescription opioid misuse and overdose fatalities is evident to the dangers of these medications. According to the 2016 National Survey on Drug Use and Health, an estimated 11.8 million people misused opioids in the previous year [1]. Factors such as diagnosis distress, invasive procedures, as well as pain related to therapies can make cancer study participants undergoing therapies vulnerable to opioid misuse [2-4]. Postoperative prescription opioid misuse is well-documented in the literature. About 6% opioid-naive study participants undergoing noncancer procedures develop new persistent opioid use [5]. For study participants with cancer undergoing curative-intent surgery, the risk of new persistent opioid use is 10.4% [6].
As for many types of surgery, opioids are used for pain control after mastectomy and breast reconstruction. Marcusa et al. utilized health benefits claims to identify 4,113 women who underwent mastectomy for breast cancer and immediate breast reconstruction between 2010 and 2014. All study participants were opioid-naïve. Based on the pharmacy claims data after breast reconstruction, 90 percent of study participants filled an opioid prescription. Ten percent of these women continued to fill an opioid prescription three months later. For women diagnosed with anxiety and those who experienced some type of complication (such as infection) prolonged opioid use was more common [7].

Most opioid prescribing guidelines focus on study participants with chronic pain, rather than postoperative pain. To our knowledge, there is no guidelines for opioids prescription following mastectomy and reconstruction procedures.

Rising rates of opioids prescription contribute to the opioid epidemic. The threat of dependence and prolonged use of opioids prescribed after surgery cannot be overemphasized. Alternative, non-pharmacological interventions to control pain after surgery seem to be the best approach to address this problem. Virtual Reality (VR) can be a viable approach.

VR provides immersive, realistic, three-dimensional experiences that “transport” users to novel environments. Thus, it has the potential to alleviate negative aspects of care by providing multi-sensory information and allowing study participants to “escape” to pleasant locations and realities when they are most distressed. VR offers an ability to temporarily alter the way study participants experience their environment, facilitating distraction from symptom triggers, increasing sense of control, and providing a safe coping mechanism. By providing an alternative to excess opioid use for pain, VR may not only ameliorate acute symptoms, but also diminish opioid-related adverse effects such as overdose and opioid use disorder, and reduce hospital length of stay.
Feasibility of VR interventions in a medical setting has been documented in the literature [8]. To our knowledge, effects of VR in controlling pain and study participant’s satisfaction for women undergoing mastectomy followed by implant-based reconstruction has not been studied.

2.0 STUDY OBJECTIVES

Primary Objectives

2.0.2 To estimate the effect of utilizing VR on reducing opioid use in study participants undergoing mastectomy with implant-based reconstruction compared to the control group

2.1 Secondary Objectives

2.1.1 To evaluate the effects of VR upon:
a) Pain scores
b) Study participant satisfaction
c) Length of stay

2.2 Endpoints

- **Primary Efficacy Endpoint**
  Opioid use

- **Secondary Efficacy Endpoints**
  Pain score
  Patient satisfaction
  Length of stay

3.0 STUDY DESIGN

We will conduct a pilot study of VR non-opioid management for women undergoing mastectomy and implant-based reconstruction. Study participants will receive specialized VR interventions, administered via VR headsets, to manage pain.

Historical control patients of the study investigators, who have undergone mastectomy and implant-based reconstruction between October 2008 to October 2018, will be identified by the Cancer Registry, according to the study eligibility criteria, and matched based on the following criteria:

- Age and gender
- Prophylactic or cancer
- Pre- or post-pectoral approach
- Sentinel biopsy, axillary dissection, or no nodal surgery
- Use of Paravertebral Block Analgesia (PVB)
- Neoadjuvant therapy or not

The matching will be done by the study statistician. Prior to sending the log to the statistician, the Cancer Registry database will be deidentified by the study staff and coded to ensure patient confidentiality. This portion of the study this is a retrospective data analysis and a waiver of consent and HIPAA authorization will be requested to review and collect data from these patients' medical records.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Age ≥ 18 years

4.1.2 Women who plan to undergo mastectomy and implant-based reconstruction

4.1.3 Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

4.1.4 Able to read and comprehend English

4.2 Exclusion Criteria

4.2.1 Current diagnosis of epilepsy, dementia, or other neurologic disease that may prevent use of VR headset and software

4.2.2 Sensitivity to flashing light

4.2.3 Diagnosis of motion sickness

4.2.4 Pregnancy or a medical condition where the study participant is prone to frequent nausea or dizziness

4.2.5 Current or recent (less than 6 months) use of opioids

4.2.6 Individuals with psychiatric disorders, including those with delirium or other disorders that may involve hallucinations or psychosis

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

5.1.1 Pre-op visit:
Eligible women will sign the study consent form at one of their pre-operative appointments. During this visit, a study staff member will explain the use of the VR goggle set by watching a short VR experience of swimming with dolphins, lasting approximately 2 minutes. The study participant and/or a member of their family will be shown how to use the device and how to recharge the battery, if needed. At this time, the patient will be offered the opportunity to test a VR set. Study participants will be advised that standing puts them at risk for a fall, and that they should remain seated for each VR intervention. An interval of 15 minutes is suggested for first-time use, but study participants will be allowed to continue as long as they are not experiencing any discomfort or side effects (dizziness, motion sickness, etc.).

We will keep a log of reasons for eligible patients who decline study participation.

5.1.2 After surgery:
After surgery, and once alert, the study participant can start using VR. The participants will be instructed to use VR the first time they feel pain and prior to requesting/taking opioids. They will be instructed to repeat that at least within 3 hours of first usage, the morning after the operation and once before discharge and any time they feel pain. Study participants will be instructed to

use the VR every time they feel pain and before asking for a pain medication. They can take pain medications, if they choose to do so.

Compliance to the protocol will be monitored using software for the VR modules and remote data uploads of activity. Additionally, study participants will be asked to log the time and duration of VR usage (appendix 2).

Pain ratings and pain medication usage history throughout hospitalization will be retrieved from the EHR by study staff. Pain rating scales and collection of medications will be done as per standard of care, and this information will then be pulled from the medical records.

5.1.3 Post-op visit:

Patient Semi-Structured Interview:
At one of their post-op visits at the Breast Center, using the provided patient interview script on Appendix 1, patients will be asked questions regarding their experience with VR. Responses will be written down by the study staff.

5.2 Use of Opioids

In order to capture medication use related to their injury, including the use of opioids, we will link patient electronic health record (EHR) data to the other data sources using Medical Record Numbers and date of birth. We will collect opioids information using. CSLINK. Prescribed opioid medications include: codeine, dihydrocodeine, morphine, hydromorphone, oxymorphone, tapentadol, buprenorphine, methadone, oxycodone, fentanyl, remifentanil, and hydrocodone. Tramadol usage will also be included. We will convert all opioid doses into a single metric using morphine milligram equivalents (MME).

5.3 Risks

Women using the virtual reality intervention may experience side effects common to users of VR and individuals who view 3D video, including motion sickness, dizziness, eye strain, headaches, or other visual abnormalities. If a study participant experiences these symptoms, she will be asked to stop using the VR software for 15 minutes and will be allowed to continue if she wishes to proceed. A small number of patients (up to 0.025%) may experience seizures or severe symptoms (e.g., disorientation, nausea, or drowsiness) upon viewing the virtual reality experience. Seizures from flashing light are more common in children and epileptic patients (who are excluded). To minimize this concern further, we have not incorporated flashing lights into the VR experiences. Some study participants may find the VR goggles uncomfortable to wear or confining. To date, patients with claustrophobia have not reported discomfort using VR goggles, as they are often used in treatment of that condition. Nevertheless, individuals previously diagnosed with claustrophobia should discontinue use if they feel uncomfortable. A trained study staff member will be available during initial use to ensure safety. Study participants who use the VR headset over several days are instructed to use it for a maximum of 30 minutes at a time. In pilot testing, patients have not reported any adverse effects from extended use of VR hardware. Subjects may feel uncomfortable when answering survey and interview questions. If subjects are uncomfortable answering any survey question, they may skip it. The survey will be labeled with a unique study number so that only the research team can identify subjects.

5.4 Duration of Study Participation

The study duration for each study participant will start prior to surgery and will end after their post-op visit once the interview has been conducted.

5.5 Subject Replacement

Subjects who withdraw from the study treatment prior to starting study intervention will be replaced.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

6.1.1 Informed Consent

Eligible subjects will be identified by the investigators and research staff according to the eligibility criteria. Subjects will be asked to sign and date the Informed Consent and HIPAA Authorization form after receiving a complete explanation of the research study including risks, benefits, and alternatives to participation. Eligible subject must have the ability to understand and the willingness to sign a written informed consent document.

6.1.2 Demographics

Name, medical record number, age, gender, race/ethnicity obtained from medical records

6.1.3 Review subject eligibility criteria

6.2 Procedures During Treatment

Pain scores will be recorded using pain scores reported to the care providers and entered in the EHR.

Opioid use will be collected via information recorded in the EHR (CS-Link).
Study participant will be approached at their post-op visit to complete study questionnaires as well as the study interview.

6.3 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

~~5~~5.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician determines continuation on the study would not be in the patient's best interest;

7.0 Virtual Reality

7.1 We will use a Samsung Gear VR goggle set, fitted with a Samsung Galaxy phone that delivers VR images and sound. Samsung Gear was selected because it is commercially available, widely used, relatively inexpensive, has minimal visual latency, and offers a generally positive patient experience based on our previous research. [8]

We will use the appliedVR app to offer >30 therapeutic VR experiences through the headsets. Our team has worked with appliedVR to curate experiences that are acceptable to a wide range of patients. The app includes a menu of visualizations, each mapped to a therapeutic benefit (e.g. pain reduction, anxiety reduction, mindful meditation).

The app includes “Pain RelieVR”, a 15-minute VR experience specifically designed to treat pain in patients with limited mobility. Pain RelieVR is an immersive, 360-degree game experience that takes place in a fantasy world where the user attempts to shoot balls at a wide range of moving objects by maneuvering their head towards the targets. This engaging, medium-intensity activity is free of interruption, offering the user a distracting experience designed to reduce the perception of pain. Pain RelieVR is a non-violent and non-competitive game that incorporates motivational music and features positively reinforcing sounds, animation and direct messages to patients. Forward- facing action allows patients with limited mobility to engage without having to turn backwards or contort into potentially uncomfortable positions.
The app also includes “Anxiety RelieVR,” an interactive, meditative landscape along a peaceful shoreline. In contrast to Pain RelieVR, which acts through distraction therapy, Anxiety RelieVR employs mindful meditation to help manage the affective component of pain. These cornerstone experiences are supported by a wide range of additional therapeutic journeys, including an Iceland flyover in a helicopter, an undersea experience, and a variety of nature-related experiences, among many others.

Another option is “EaseVR” which is a new meditation VR experience that is currently being used in several pain studies within Cedars-Sinai and beyond. During the program the patient can be in 8 different environments while a narrator who is an expert in meditation walks through the experience. The patient will have a microphone to deep breath with the meditation program.

Patients can pick and choose which visualizations to watch based on their own preferences. In clinical testing, we asked patents to use the headset at least thrice daily, for 15 minutes per treatment period, and to also use as needed for breakthrough pain between treatments. The appliedVR software allows our team to monitor adherence with the therapy, including the visualizations selected by the user, the amount of exposure time, and the time of day the visualization was viewed.

Using Samsung Gear goggles, participants will be shown a short VR experience of swimming with dolphins, lasting approximately 2 minutes. During your pre-op visit, a study staff member will show the participants how to use the VR goggles and connected smartphone and answer any questions about them.

They will be asked to watch VR only once after they wake up after surgery, and any time they feel pain. We recommend taking short, 5-10-minute breaks after 30 minutes of use, but they may continue afterward. This experience is an addition to usual care in the hospital and will not impact any additional care the participants receive at CSMC.

We will also obtain pain ratings, participants’ use of pain medication while recovering from the surgery, and any physical symptoms they report to the nurse throughout your stay. Recording all of this information is standard of care. It is not being done for research. We will review medical records to obtain this type of information.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size

This is an exploratory pilot study to estimate the effect of VR on opioid use during the stay. We will enroll 20 eligible patients to this study. We will include data from 20 patients for the historical control portion of the study matched 1 to 1 on age, surgery type, use of neoadjuvant therapy, and use of paravertebral block analgesia. Assuming a standard deviation of 1, a sample size of 20 matched pairs would produce a confidence interval with a distance from the mean to the limits that is equal to 0.468 for the difference in requested pill count.

9.2 Data Analyses/Study Endpoints

Quantitative data will be expressed as mean ± standard type or median with interquartile range, and categorical variables as counts and frequencies. We will use complete case analysis to manage missing data. All statistical analyses will involve the use of Excel. Descriptive statistics will be used to summarize pain scores and opioid use in the intervention and the historic control group. Average number of opioid pills requested will be compared between the study cohort and the historic control group. A paired t test will be used to compare the difference in average pill count between the two groups based on the matched pairs with historic controls. Confidence intervals for the number of pills and the secondary endpoints of reported pain scores, satisfaction, and length of stay will be calculated in the study cohort and for the historic controls.

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.3 Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Assignment of Subject ID: The study team will track all subjects who sign consent on a subject screening/enrollment log using a unique screening ID (S001, S002, etc.). Subjects found to be ineligible will be recorded as screen failures.

Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the investigators. The following documents will be completed and provided for review:

- Registration form (or equivalent)
- Copy of applicable source documents
- Eligibility checklist (signed by investigator)
- Signed patient consent form and Subject's Bill of Rights
- HIPAA authorization form

Oversight by the principal investigator is required throughout the entire registration process

9.4 Data Management and Quality Control and Reporting

Data will be entered into a HIPAA-compliant database. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Data collected from medical record, such as opioid prescriptions and physician history, will reside on secure CSMC servers and an ID will be assigned to each individual in order to abstract PHI and the medical record number. Each dataset will utilize different unique ID's and a list linking each unique ID to each participant will be stored internally on the secured CSMC network. The linking list allows a researcher with access to the secured files to merge all data using statistical software, while maintaining data confidentiality.

10.0 REFERENCES

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APPENDIX 1

Qualitative Interview

Patient Interview Script

We want to thank you for your participation in the study and for agreeing to talk with us today. This interview will take approximately 10-15 minutes, and we will ask you several open-ended questions about your thoughts and feelings about wearing the Virtual Reality device and "participating" in the experiences. There are no 'right' or 'wrong' answers to any of these questions: we want to hear about your experience and listen to your opinion, in your own words.

General "Think Aloud" Probe
When you think about your experience participating in the Virtual Reality study, what is the first thing that comes to your mind?

Participating in the Intervention:
Would you like to participate in a study like this one again? Why?

How did participating in this study make you feel?
(PROBES: distracted, happy, confused, dizzy, anxious, at ease, etc.)

The VR Device:
If a friend or family member asked you about the device, what would you tell them about it?

How comfortable were you wearing the device?

Did you have any concerns about the device while you were using it? If so, what were they?

Did you have any questions about the device while you were using it? If so, what were they?
(Researcher should record if patient asked questions while using it)

Do you have any thoughts on how the device can be improved?

VR Experiences:
From what you watched, which did you like the most? Why?

From what you watched, which did you like the least? Why?

What was your favorite part about watching the ‘experiences’?

What was your least favorite part about watching the ‘experiences’?

What did you think about the duration of the ‘experiences’? Were they too long? Too short?

What would be your ideal ‘experience’ duration? (e.g. how many minutes long would you want them to be)

If at all, how do you think the ‘experiences’ can be improved?

What would you like to see in additional ‘experiences’?

Would you recommend the Virtual Reality to your family and friends?

Perceived Effects of Participation:
[IF ANXIETY IS A CONCERN:] Do you think that wearing the device affected your anxiety level? [IF YES:] How so?

Do you think that wearing the device affected your pain? [IF YES:] How so?

These are all the questions we have for you today. Is there anything we didn’t mention that you would like to discuss?

Thank you again for your participation in this study, and please feel free to contact our research coordinator if you have anything else you would like to discuss with us about this project.

APPENDIX 2

VR Experience Tracking Log

How many times did you watch Virtual Reality DATE	None	Once	Twice	Three times	Four times	More than four times
	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐