IRB #XXXXXX

The Role of a Virtual Reality Intervention on Postoperative Pain (REVEAL-Pain Study)

Sponsored by:

National Institutes of Health (NIH)

Department of Biostatistics, University of Washington

Principal Investigator (PI):

Unmesha Roy Paladhi, MPH

University of Washington, Seattle WA

617-306-5564

uroy@uw.edu

Co-Investigators (Co-PIs):

Savannah Bifulco
University of Washington,
Seattle WA
850-637-5449
sbifulco@uw.edu

Jie Wang, MPA
University of Washington,
Seattle WA
206-484-8386
jwang18@uw.edu

Pinyan Liu, BS
University of Washington,
Seattle WA
206-209-7501
pliu5@uw.edu

Protocol Version: V1.0.20200601

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
CP	Chronic Pain
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practices
IRB	Institutional Review Board
NIH	(United States) National Institutes of Health
SAE	Serious Adverse Event
VR	Virtual Reality
NRS-11	Numeric Rating Scale
PHQ-9	Patient Health Questionnaire
PROMIS	Patient-Reported Outcomes Measurement Information System
CSF	Cerebrospinal Fluid
UWMC	University of Washington Medical Center

PROTOCOL TEAM ROSTER

Unmesha Roy Paladhi, MPH
Principal Investigator
University of Washington
617-306-5972
uroy@uw.edu

Jie Wang, MPA
Co-investigator
University of Washington
206-484-8386
jwang18@uw.edu

Savannah Bifulco
Co-investigator
University of Washington
850-637-5449
sbifulco@uw.edu

Pinyan Liu, BS
Co-investigator
University of Washington
206-209-7501
pliu5@uw.edu

INVESTIGATOR SIGNATURE PAGE

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the final Continuing REview after conclusion of the trial unless otherwise specified by the Institutional Review Board (IRB). Any presentation, abstract, or manuscript will be made available by the investigators to all co-authors for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

SCHEMA

Purpose

The purpose of this study is to evaluate the use of a virtual reality (VR) intervention in the reduction of incidence of chronic pain post-orthopedic surgery. The secondary outcome is to evaluate potential depression, anxiety, and opioid use in patients during a 6 month recovery period.

Design

This study is a phase 2 placebo-controlled randomized trial to evaluate a VR intervention in a post-operative orthopedic surgery setting. Participants will be recruited from the University of Washington Medical Center (UWMC) orthopedic surgery department if they are scheduled to have elective orthopedic surgery or from the emergency or trauma departments if they are identified as needing emergent orthopedic surgery and randomized to either the VR intervention or control arm. Biosamples and questionnaires will be used to measure pain levels from the time of surgery to six months post-operative in order to assess any changes in pain conversion from acute to chronic pain, anxiety and depressive symptoms, and opioid use patterns.

Study Population

Patients with elective or emergent orthopedic surgery presenting at the University of Washington Medical Center (UWMC).

Study Size

A total of 100 participants may be recruited to yield a total of 80 evaluable participants- 40 participants per study arm.

Treatment Regimen

Participants randomized to the study intervention will receive a VR intervention and control participants will receive a web-based health and wellness TV channel.

Study Duration

Study participation will last approximately 6 months per participant, beginning from the day of their orthopedic surgery and the study will aim to be completed in 3 years.

Primary Objective:

· To determine if the use of a VR intervention reduces the conversion of acute to chronic pain after orthopedic surgery as measured by an 11-point Numeric Rating Scale (NRS-11) of pain intensity from PROMIS pain measures

Secondary Objectives:

· To measure changes in pain-linked biomarker expression levels of transient receptor potential cation channel subfamily A and V member 1 (TRPV1 and TRPA1) and metabolites in the kynurenic acid pathway to assess neurogenic inflammation in post-operative pain patients

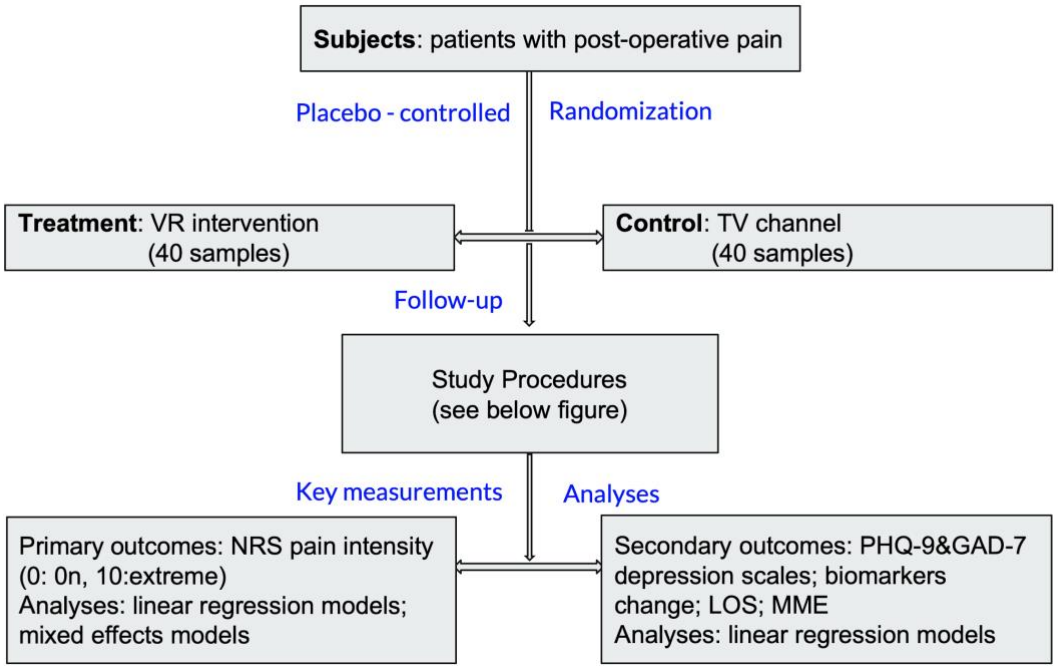
· To measure changes in depression and anxiety as short-term (7 days) and long-term (6 month) outcomes of orthopedic surgery using the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) scale as well as TRPV1 and TRPA1 expression levels

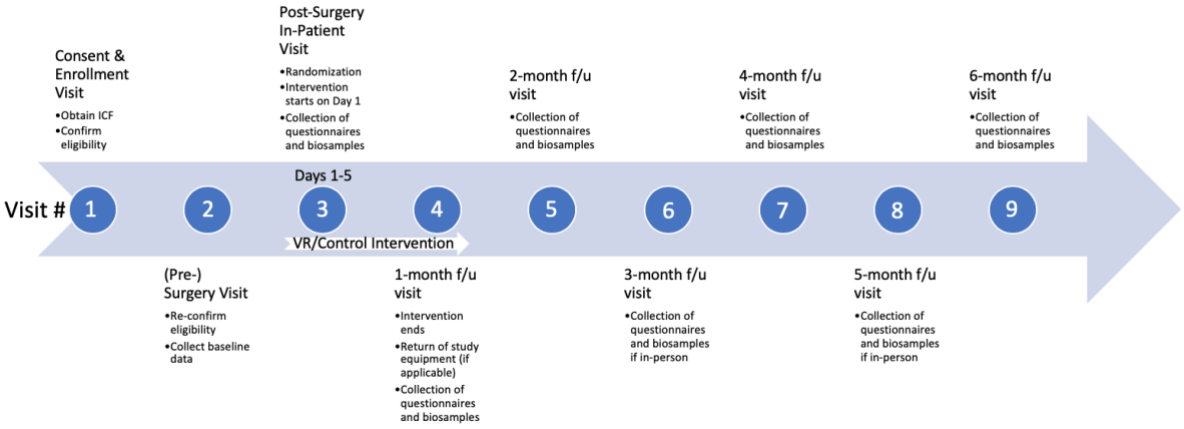
· To study short-term (7 days) and long-term (6 months) changes in opioid usage patterns in post-orthopedic surgery patients using morphine milligram equivalents (MME) and self-reported outcomes

Study Site

University of Washington Medical Campus

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION





1.0 INTRODUCTION

1.1 Background and Prior Research

The prevalence of complex regional pain syndrome, phantom limb pain, chronic donor-site pain, and long-standing chronic pain following a wide range of orthopedic surgeries are alarmingly high. Specifically, Chronic post-operative pain occurs in approximately 10% of patients that undergo surgery and often stems from uncontrolled acute pain during the post-surgery recovery period[1]. In particular, orthopedic surgery such as hip and knee replacements have a high prevalence of persistent pain after surgery.[9] When this pain exceeds six months, it transitions to chronic pain, demonstrating the need for interventions to prevent this acute condition to its chronic counterpart. Additionally, rates of depression and anxiety are higher in the post-operative population compared to the general population[6], and can lead to a lower threshold for pain and suppression of the immune system, leading to a longer recovery time after surgery[5].

Based on all clinical conditions, there are various prevalence estimates depending on the case, the sampling method and the timing of the postoperative assessment. Macrae and Davies[10] in 1999 were the first to propose specific criteria which should be satisfied in order for chronic pain to be defined as post-surgical.[2]

- The pain must develop after a surgical procedure.
- The duration of the pain is at least two months.
- Other causes for the pain have been excluded
- Excluded the possible pain from a pre-existing condition.

The assumption of these definitions is under the constant pain experience, whereby acute postoperative pain continues to eventually become chronic. However, it has been shown in empirical studies that in the acute postoperative period a proportion of patients are pain-free or just have mild pain, compared with new onset pain developing a period of time after the initial surgical insult.

Due to this critical and painful period of recovery, patients are often prescribed opioids, which are a class of drugs that include the illegal drug heroin, synthetic opioids such as fentanyl, and pain relievers available legally by prescription, such as oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, morphine, and many others. The continued and prolonged usage of these drugs may lead to a loss of responsiveness which may lead to uncontrolled pain with neuropathic indications and dependence on opioids. Additionally, rates of depression and anxiety are higher in the post-operative population compared to the general population[6], and can lead to a lower threshold for pain and suppression of the immune system, leading to a longer recovery time after surgery[5].

The prevalence of opioid dependency, now coined “the opioid epidemic”, has led to the exploration and testing of many non-pharmacological interventions. VR interventions have successfully been used in previous studies to manage pain,[2] improve cognitive outcomes after traumatic brain injury,[3] enhance quality of life after stroke,[4] and reduce cancer-related psychological symptoms.[9] Most recently, a VR intervention was able to successfully reduce acute pain in hospitalized patients[7]. While these types of VR interventions are relatively new in the field of non-pharmacological pain management methods, there is a fine need to prevent the conversion of acute to chronic pain in many domains.

VR interventions have been successfully demonstrated as a useful medical tool in managing pain by previous scholars. One example is the application of VR analgesia in managing labour pain by Frey et al. (2019) in early stages of unmedicated contraction[9]. Participants in this study were treated with watching VR videos presenting underwater scenes with relaxing music. Information from this study suggests that there were significant decreases (up to 95%) in affective, sensory and cognitive pain and reduced anxiety levels. Most recently, a VR intervention was able to successfully reduce acute pain in hospitalized patients.[7] This is a prospective, randomized, comparative effectiveness trial in hospitalized patients. The goal of the study was to measure the impact of on-demand VR versus television programming of “health and wellness” for pain in hospitalized patients. In the experimental group, patients were using the Samsung Gear Oculus headsets to receive a library 21 VR experiences. While in the control group, television programming was assigned to patients to promote health and wellness. Then, they were both followed by usual care by clinical staff. The primary outcome was patient-reported pain using a numeric rating scale, recorded by nursing staff during usual care. Then, at time point 48- and 72-hours after initial treatment, pre- and post intervention were compared immediately. In conclusion, the study showed that VR significantly reduces pain versus an active control condition in a population of hospitalized patients, especially in cases of severe pain. In an attempt to replicate these results in a post-operative population that are in danger of opioid dependence due to the current standard of care, we are proposing a phase 2 placebo-controlled randomized trial to evaluate a targeted VR intervention in a post-operative orthopedic surgery setting.

While these types of VR interventions are relatively new in the field of non-pharmacological pain management methods, there is a fine need to prevent the conversion of acute to chronic pain in many domains. In addition to reducing chronic pain in our patient population, we will also be measuring known symptoms that coincide with chronic pain, including self-reported opiate usage, self-reported depression, length of hospital stay, as well as significant biomarkers linked to chronic pain and depression for an impartial analysis.

The increasing quality and affordability of portable VR headsets and the continuing utility of pain therapy predict a bright future for the use of VR for analgesia. However, whether VR interventions have long-term effects on relieving pains is still under investigation. Our team has extensive experience in the field of chronic pain and the intersection of technology and health,

and thus we intend to use our combined expertise to conduct this novel clinical trial. This study is an important step in tackling the global opioid crisis and contributes significantly to understanding VR technology's role in preventing chronic pain.

1.2 Rationale

Patients who have undergone orthopedic surgery commonly experience acute and/or chronic moderate to severe pain, leading to increased rates of depression and opioid abuse. Palliative care is a medical subspecialty that aims to relieve pain and suffering of such patients through pharmacologic and non-pharmacologic therapies. Those receiving inpatient palliative care consultations for pain management typically only receive drug therapies for analgesia, likely opioids. The current nationwide opioid epidemic highlights serious risks associated with prolonged opioid usage. Ideally, we could replace opioids with non-pharmacologic pain management methodologies. Clinical literature and expert opinion underline the importance of utilizing such non-pharmacologic therapies to maximize relief without additional side effects.[15] However, many of these pain management strategies are not reimbursed by insurance, limiting use to those with disposable financial resources. One such non-pharmacologic intervention, virtual reality (VR), continues to demonstrate effectiveness in pain management.[16] VR is a rapidly developing technology that temporarily immerses the subject in a calm, pleasant environment, providing distraction from pain and lowering pain sensation. While the pathophysiology of pain is complex, such non-pharmacologic interventions seem to modulate pain by reducing the level of attention paid to noxious stimuli, thereby suppressing transmission of painful sensations to the cerebral cortex.[17] In the face of the rising national opioid epidemic, we, as clinicians and investigators, must develop and implement new strategies to address pain and suffering without increasing risk to the patient. As such, we believe this study is important for several reasons: a) the presence of chronic pain underlies the necessity for interventions regarding acute and chronic pain management; b) patients are in need of non-pharmacological options for pain management; c) health insurance plans rarely provide reimbursement for non-pharmacologic pain management interventions, leaving patients to provide their own resources; d) VR technology is rapidly evolving into both a more immersive and more widely available experience.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objective of this study is to:

- Determine if the use of a VR intervention reduces the conversion of acute to chronic pain after orthopedic surgery as measured by an 11-point Numeric Rating Scale (NRS-11) of pain intensity from PROMIS pain measures

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Measure changes in pain-linked biomarker expression levels of transient receptor potential cation channel subfamily A and V member 1 (TRPV1 and TRPA1) and metabolites in the kynurenic acid pathway to assess neurogenic inflammation in post-operative pain patients
- Measure changes in depression and anxiety as short-term (7 days) and long-term (6 month) outcomes of orthopedic surgery using the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) scale as well as TRPV1 and TRPA1 expression levels
- Study short-term (7 days) and long-term (6 months) changes in opioid usage patterns in post-orthopedic surgery patients using morphine milligram equivalents (MME) and self-reported outcomes

2.3 Study Design

This study is a phase 2 placebo-controlled randomized trial to evaluate a targeted VR intervention in a post-operative orthopedic surgery setting. Participants will be recruited from the University of Washington Medical Center (UWMC) orthopedic surgery department if they are scheduled to have elective orthopedic surgery and from the emergency or trauma departments if they are identified as needing emergent orthopedic surgery. Once they are identified, they will be approached for informed consent prior to surgery, if possible. If the surgery is emergent and there's no opportunity for informed consent prior to surgery, consent will be obtained as soon as possible after surgery has been performed.

Participants will be administered a comprehensive baseline questionnaire consisting of an 11-point numeric rating scale (NRS-11) of pain intensity, PHQ-9, and GAD-7 scale. Baseline blood and if possible, CSF sample, will also be collected. After obtaining consent and completion of all baseline procedures, participants will be randomized to either the VR intervention or control arm to complete their study participation.

To those randomized to the intervention arm, a study team member will explain the intervention and how to operate the VR headset, including proper wearing etiquette, picking from the channel options, and adjusting volume and brightness. To those randomized to the control arm, the team member will inform them of the television (TV) channel where health and wellness information is broadcasted. Both groups will be instructed to continue with their recovery as prescribed by their surgeon and to either avail the VR intervention or TV channel (as randomized) as frequently as they would like

to help relieve any feelings of pain during the remainder of their hospital stay. Of note, the health and wellness TV channel will not be available to the intervention group. Usage of interventions will be recorded by participants and verified by study staff during compliance checks.

During the first 5 days post-surgery or until discharge (whichever comes first), not inclusive of the day of surgery, daily blood samples will be collected prior to the first meal and/or VR experience of the day. An NRS-11 questionnaire will be administered daily for 5 days. On Day 1 and Day 5 post-surgery, participants will be asked to complete the PHQ-9, and GAD-7 scale questionnaires. Lastly, a CSF sample will be collected on Days 2 and 5 after surgery, if possible.

After discharge, participants will be followed up for 6 months, on a monthly basis, since their surgery to monitor their recovery and long-term effects of their intervention. These visits will be planned around regular clinical follow-up visits for their post-surgery check-ups to avoid additional hospital trips. During the first month post-discharge, participants will be provided with the same VR headset or link to the health and wellness TV channel to take with them and use at home, pro re nata. Participants will be asked to keep a diary of the frequency and duration of their intervention usage during this outpatient period, and report any adverse effects they may feel during this time. During the 1-month follow-up visit, participants will be asked to submit their diary to the study team. To ensure adherence, the study team can call participants in both arms on a bi-weekly basis to ask about their intervention usage habits.

3.0 STUDY POPULATION

Orthopedic surgery patients will be included in this study. Participants will be selected for the study according to the criteria in Section 3.1 and 3.2 in addition to the guidelines in Section 3.4. They will be recruited, screened, and enrolled as described in Section 3.3 and assigned to a study intervention group as described in Section 7.4. Issues related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively.

3.1 Inclusion Criteria

Adults who meet all of the following criteria are eligible for inclusion in this study:

- Ages 18-65
- Minimum pain threshold of 3 as measured by their NRS score
- Patients undergoing elective surgery including arthroscopy, soft tissue repair, joint replacement, bone fracture repair, and osteotomy

3.2 Exclusion Criteria

Adults who meet any of the following criteria will be excluded from this study:

- Previously diagnosed acute or chronic pain conditions including chronic lower back pain (CLBP), fibromyalgia, migraine, etc.
- Blindness, as the VR experience is untested in this population
- Current or previous substance use disorder
- History of motion sickness or vertigo
- Pregnancy
- Unable to provide informed consent
- Unable to understand written English at the 8th-grade level
- Student, colleague, or relative of any of the Investigators
- Others, at the discretion of the Investigators

3.3 Recruitment Process

Study team members will utilize the electronic health record system, Epic, to screen for potentially eligible participants in the orthopedic surgery department on a weekly basis. They will also screen the emergency and trauma departments for emergent orthopedic surgery cases on a daily basis. Orthopedic surgery and emergency providers at UWMC will also be trained on the study protocol to enable direct referrals from their practices.

Once participants are identified, they will be approached in the clinic when they are at UWMC for a pre-surgery appointment to obtain informed consent. For emergent cases, study staff may ask to speak with potential participants when they are not actively receiving life-saving medical care. Once informed consent is obtained, study procedures can proceed as described in section 5.0.

3.4 Co-Enrollment Guidelines

Participants may not enroll or participate in any concurrent clinical trials while participating in this study.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain them for 6 months of follow-up in order to minimize possible bias associated with loss-to-follow-up. After discharge of participants post-surgery, participants will be provided with a $20 incentive for every follow-up visit they attend and complete study procedures (since CSF is optional, it is not necessary to receive the incentive). A bonus of $100 will be provided if the patient does not withdraw from the study prior to 6 months of participation and completion of all study procedures.

Participants will also be provided with a calendar of all their study visits for 6 months prior to starting the study and additionally receive email and/or text reminders of their visits close to their visit dates. In the event of a missed visit, participants will be contacted by study staff to reschedule within 5 business days.

3.6 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The Investigators also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or IRBs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Section 5.0) of participants who terminate from the study prior to 6 months, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY INTERVENTION

4.1 Intervention Formulation

VR intervention
The VR experience consists of using the Samsung Gear Oculus headset fitted with a Samsung Galaxy S7 smartphone. The smartphone includes an application (appliedVR) with a choice of 21 different VR experiences. The Samsung Gear is widely used, commercially available, relatively inexpensive, has minimal visual latency, and offers an acceptable patient experience based on previous research. After randomization to the experimental arm, participants will be instructed on procedures for wearing the headset and how to select among 21 VR experiences from an application on the phone's menu (appliedVR; Los Angeles, California). They will be provided an opportunity to practice with the equipment, then suggested to use the headsets three times daily, with each use limited to 10 minutes. 10 minutes per session reduces the risk of developing cybersickness. A list of VR and 360-video experiences offered to participants is shown in the table below. There are 5 main types of VR experiences, each with 3-4 subtypes which may have different levels and settings.

Title	Content Description	Screenshot
Guided Relaxation	Look around a scenic mountain and ocean environment while being guided through meditations.	
Water Boating	Boat in the rushing torrents of the river while avoiding obstacles.	
Wright Flyer	Allow the viewer to fly a 1905 Wright Flyer over the prairie.	
Desert Survival	Find different types of food including water, bread and meat to ensure survival before time runs out.	
Feeding Chicken	Launch different types of food to feed hungry chicken to meet the different criteria.	

Control intervention
Current "standard of care" is to rest in bed after surgery. However, with the possibility of the Hawthorne effect of the VR intervention, the control arm will be provided with access to a health and wellness TV channel, available via a website link as an alternative to the VR intervention. It has regularly scheduled meditations, relaxation and breathing exercises, and health and wellness 'tips' for patients post-surgery.

Of note, these interventions are not a replacement for post-surgery opioid administration, and all normally prescribed medications will continue. However, we will ask the hospital staff to not dispense the prescribed medications for pain until specifically requested by the study participants.

4.2 Intervention Regimen and Administration

VR intervention
When the study participant is fully alert after waking up post- surgery, they will receive a VR phone headset, as well as instructions from the research team on how to use the equipment. They will also be instructed to discuss use with their care team to adjust usage as necessary. The same VR headsets will also be allowed to be taken home for 1 month following discharge to study long-term outcomes. Participants will be asked to use the headset for 10 minutes, 3 times a day (prior to meals) and at least 3 days per week while in the hospital and at home, pro re nata.

Control intervention
Participants will be instructed to watch the TV channel via weblink for 10 minutes, 3 times a day (prior to meals) and at least 3 days per week in the hospital and at home, pro re nata. The same website links will be active for participants to use at home during a 1-month follow-up period.

4.3 Intervention Supply and Accountability

All study materials including VR headsets, smartphones, and web-based TV programming will be provided by the study. All study materials must be signed-out to participants and signed back in at the conclusion of their study participation. Participants that don't return study VR headsets or smartphone devices may receive a bill from the University of Washington for up to $5,000.

4.4 Adherence Assessment

Intervention use will be recorded by both floor medical staff (nurses/ MAs) and self-reported by participants on study case report forms (CRFs).

4.5 Safety Management

Participants' healthcare providers (in collaboration with the study team) have full authority to modify the intervention regimen as they see fit if the participant is experiencing side effects of the VR experience such as nausea or fatigue. Promethazine may be taken by participants if they experience nausea or vomiting. If the symptoms significantly worsen their condition

4.6 Clinical Management of Pregnancy

Pregnant individuals are excluded from the study. Those that become pregnant during the course of their study participation will be monitored until their study participation is complete, though the study intervention will be immediately stopped.

4.7 Concomitant Medications

Enrolled study participants may continue use of all concomitant medications during this study, including those prescribed ad lib during the surgery recovery period. All concomitant medications taken or received by participants within the 4 weeks prior to study enrollment will also be reported on applicable study case report forms. In addition to prescribed and over-the-counter medications vitamins, herbal remedies, and other traditional preparations will be recorded. Alcohol and recreational or street drug use will be recorded in study CRFs. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable CRFs.

5.0 STUDY PROCEDURES

Presented below is a detailed description of all visit-specific study procedures:

Visit #	Visit Description	Visit Procedures	Biosamples Collected	Data Collected
1	Consent and Enrollment Visit	Obtain informed consent	None	-ICF -Eligibility form -Concomitant meds form
2	(Pre-)Surgery Visit	Participants' eligibility will be confirmed via the baseline questionnaire and asking for self-report of pregnancy.	None	-Baseline questionnaire including NRS-11, PHQ-9, and GAD-7 -Concomitant meds form

3	Post-Surgery In-patient Visit (Days 0-5)	Day 0: randomization to intervention Days 1-5: NRS-11, blood Days 1 & 5: PHQ-9, GAD-7 Days 2 & 5: CSF (optional)	-Blood -CSF (optional)	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update -AE form -Intervention diary
4	1 Month Follow-up	This is the first follow-up visit. Participants will be asked to return all study VR equipment at this visit.	-Blood	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update -AE form update -Intervention diary update
5	2 Month Follow-up		-Blood -CSF (optional)	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update -AE form update -Intervention diary update
6	3 Month Follow-up	This visit can be conducted remotely via phone by study staff or in-person if participant has a scheduled clinic follow-up. If remotely conducted, blood won't be collected.	-Blood	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update -AE form update -Intervention diary update
7	4 Month Follow-up		-Blood -CSF (optional)	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update

				-AE form update -Intervention diary update
8	5 Month Follow-up	This visit can be conducted remotely via phone by study staff or in-person if participant has a scheduled clinic follow-up. If remotely conducted, blood won't be collected.	-Blood	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update -AE form update -Intervention diary update
9*	6 Month Follow-up	This is the final study visit so an additional exit interview will be conducted at this visit to record participant experiences, adherence, and feedback on the trial.	-Blood -CSF (optional)	-NRS-11 -PHQ-9 -GAD-7 -Concomitant meds form update -AE form update -Intervention diary update -Exit interview

*If a participant withdraws during the course of the study post-randomization, Visit 9 should be conducted and reasons for withdrawal will be collected as part of the exit interview.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

The study Investigators are responsible for continuous close monitoring of all adverse events (AEs) that occur among study participants, and for alerting the rest of the protocol team if unexpected concerns arise. Accrual will be suspended if two or more study participants experience a grade 3 or higher AE judged possibly, probably, or definitely related to intervention. The protocol team then will review all pertinent safety data and determine whether to continue accrual and intervention. A decision to stop the trial may be made by the protocol team at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

6.2 Adverse Event Definitions and Reporting Requirements

6.2.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an intervention and which does not necessarily have a causal relationship with the intervention. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the administration of an intervention, whether or not considered related to the product.

Study participants will be provided a 24-hour telephone number and instructed to contact the study staff to report any AEs they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Study site staff will document on study case report forms all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study intervention. The investigator or designee will assess the relationship of all AEs to the study intervention based on their clinical judgment.

6.2.2 Serious Adverse Event

Serious adverse event (SAE) will be defined per U.S. Code of Federal Regulations (CFR) 312.32 and International Conference on Harmonization (ICH), "Good Clinical Practice: Consolidated Guidance" (E6) and "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (E2A), as AE occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization

This includes important medical events that may not be immediately life-threatening or result in death, or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

The purpose of this study is to investigate the use of a virtual reality intervention in the reduction of incidence of acute and chronic pain in a post-orthopedic surgery setting. It is formulated as a phase 2 placebo-controlled randomized trial to evaluate a targeted VR intervention in a post-operative orthopedic surgery setting.

7.2 Endpoints

Primary

- NRS-11 pain intensity scores

Secondary

- Length of hospital stay
- PHQ-9 and GAD-7 scores
- Morphine Milligram Equivalents
- TRPV1 and TRPA1 expression levels
- [OPTIONAL] Kynurenic acid levels

7.2.1 Primary Endpoints

Consistent with the primary study objective to assess the effectiveness of VR intervention in reducing the incidence of chronic pain, the following endpoint(s) will be assessed:

- Pain Intensity Scores (NRS-11)
  The primary outcome will be pain intensity collected by self-reported participant data. Everyday during their hospital stay, at 2pm subjects will be asked by study staff to rate their pain using a standard 11-point numeric rating scale (NRS), where 0 is “no pain” and 10 is “worst imaginable pain”. Data will be summarized as mean and time-series data. Outcomes from the VR intervention arm will be compared to outcomes from the control arm.

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to determine if the use of a VR intervention reduces chronic pain after orthopedic surgery, the following endpoint(s) will be assessed:

- Length of Stay (LOS)
  Defined as the number of days from the date of admission to date of hospital discharge. Patients admitted late on Day 0 (i.e., before midnight), and discharged the following calendar day (i.e., between 00:00 and 23:59), will be counted as a 1-day hospital stay.

Patients who were admitted and discharged on the same calendar day were considered to have an LOS of 0.

- Patient Health Questionnaire- 9 (PHQ-9)
  The PHQ-9 is a self-administered validated, standardized instrument to monitor the severity of depression and response to any treatment. It scores 9 DSM-IV criteria for depression on a scale from "0" (not at all) to "3" (nearly every day). By administering the questionnaire before initiating any intervention and comparing it to both short-term and long-term timepoints, we will be able to assess if the proposed intervention has any effect on post-surgical depressive symptoms.

- Generalized Anxiety Disorder 7-point (GAD-7) scale scores
  The GAD-7 scale is a self-administered, validated, instrument to monitor the severity of anxiety and response to treatment. It scores 7 criteria for anxiety on a scale from "0" (not at all) to "3" (nearly every day). This scale works well with the PHQ-9, which is also administered in this study. By administering the questionnaire before initiating any intervention and comparing it to both short-term and long-term timepoints, we will be able to assess if the proposed intervention has any effect on post-surgical anxiety symptoms.

- Morphine Milligram Equivalents (MME)
  Opioid usage will be defined in the proposed clinical trial as mean total milligrams of morphine equivalent (MME). This value will be calculated by multiplying the quantity of each prescribed medication by the strength of that medication, and then multiplying this quantity-strength product by conversion factors derived from published sources to estimate the milligrams of morphine equivalent to the opioids dispensed in the prescription. The mean post-intervention MME for patients within each arm of the trial will be calculated by adding the morphine equivalents for each prescription dispensed during the 72 hours post intervention. The mean post-intervention MME usage will be compared between treatment arms. MME will also be observed long-term for the duration of the participant's study participation. Similarly, the mean chronic post-intervention MME usage will be obtained and compared between treatment arms.

- TRPV1 and TRPA1 expression levels
  Transient receptor potential (TRP) channels play key roles for the transition from acute to chronic postoperative pain after surgery. To evaluate TRP channels in the peripheral blood cells as blood biomarkers for chronic pain, we will collect blood samples for genome-wide assays of the mRNA expression. We expect a significant association between increases in the number of pain symptoms and increases in the TRP vanilloid 1

(TRPV1) expression. Conversely, we expect decreases in the TRP ankyrin 1 (TRPA1) expression.

- [OPTIONAL] Kynurenic acid levels
  Collection of cerebrospinal fluid (CSF) via lumbar puncture will be performed by an attending doctor at 48 hours post-surgery. During this time, levels of kynurenic acid will be measured. Increased levels of kynurenic acid metabolite are associated with an increase in the kynurenine pathway of which is highly correlated with instances of chronic pain. Levels of Kynurenic acid in healthy individuals ranges from 0 – 2.0, while patients with chronic pain have levels of Kynurenic acid of 1.7 ± 0.9 ranging from 0 – 14.4. Lumbar punctures for the quantification of kynurenic acid and corresponding metabolites will also be performed at days 2 and 5 post-surgery as well as follow-up visits at 2 and 4 months. Comparison of metabolite levels will be compared at the acute and chronic levels within each treatment arm to observe the advancement from acute to chronic pain. Furthermore, assessment of chronic accumulation of metabolites will be performed between the two treatment arms to inform the effectiveness of the intervention in preventing chronic pain.

7.3 Accrual, Follow-up, and Sample Size

Using power calculations based on a predicted mean NRS pain score of 4.0 (SD 2.0)[13], which has been previously established as the tolerable pain threshold.[18] Assuming a change in pain score of 1.5, and targeting a power of 80% (alpha = .05 for two-sided tests), the total study sample required with these stipulations is 58, with each treatment group containing 29 participants. This calculation was performed using R, and standard formulation. Power calculations for a two sample test can be similarly obtained as this statistic also follows a standard normal distribution under the null hypothesis.

The target is a relative 1.5 decrease in NRS scores. Then, for a two-sided test, we assume a 2.5% false positive error rate, which has $z_{.975} = 1.96$; for 80% power, which means a ß=20% false negative error rate, we have $z_{.80} = 0.842$. Using the following formula:

$$N = \frac{2*(Z_{1-\alpha/2} + Z_{1-\beta})^2 V}{\Delta^2}$$

we could calculate the sample size in each group is 28, which is consistent with the results calculated by R.

With the expectation that some participants will drop out and to allow for screen failures, we will recruit up to 100 participants, with a total evaluable sample size of 80. This yields an even split of 40 participants per study arm.

7.4 Random Assignment / Study Arm Assignment

Participants will be randomly assigned (on a ratio of 1:1) to the intervention or control arm based on a pre-determined randomization scheme based on blocks of 20 and stratified by sex. The assignments will be placed in sealed envelopes which are to be stored in a locked cabinet by the study team. Envelopes will only be opened after the participant has provided informed consent and baseline samples and questionnaires have been completed.

7.5 Blinding

Participants will not be blinded to the differences between the two interventions as they will be aware which intervention they are randomized to. Furthermore, blinding of the study team is not possible due to daily tasks they have to complete. However, the Investigators and biostatisticians on the project will be kept blinded to reduce bias, unless there is a safety issue with the protocol.

7.6 Data Analysis

We will perform a randomized, comparative effectiveness trial in hospitalized patients with an average pain score of >= 4 out of 11 points. Before the inferential statistical analysis, we will calculate descriptive statistics for demographic and clinical characteristics of the sample including age, sex, race, ethnicity, and baseline pain, depression, and anxiety scores. Bivariate analyses will be used to evaluate significant differences between groups, using two-sample t-tests for continuous variables and chi-square tests for categorical variables.

7.6.1 Primary Analyses

For the primary outcome, the mean and standard deviation difference will be performed in immediate pre- and post- intervention pain scores in the VR group and in the control group separately. A robust standard error estimates linear regression model will be fit in this part. The difference in immediate pre- and post- intervention pain scores of each participant will be treated as outcomes, and study groups will be treated as predictors adjusted for age, sex, race, types of surgery, types of pain and baseline measurements of NRS-11, PHQ-9 and GAD-7. A P-value of <0.05 will indicate significant differences. Evaluation of the initial impact of the first intervention session will be performed. Then, long-term analysis will be used to test effects of interventions. Pain-scores recorded at time points daily for 5 days (or number of days until they are discharged) and monthly for the following 6 months by the study group will be compared. Because this part of the study features a repeated measures design, and considering the within-subject nature of time-series data, a mixed effects model with pain scores grouped at the subject level as the dependent variable will be used. In addition, statistical adjustment for time-invariant

variable like age and sex, race, types of surgery, types of pain, as well as baseline measurements of NRS-11, PHQ-9 and GAD-7 will be implemented. The aim is to evaluate the pain intensity change of each individual as time goes by. Once all patients have completed the 6- month trial, we will conduct an additional robust standard error estimates linear regression model. The outcome will be the difference between the baseline pain scores and the 6th month measurement, and the predictor will be study groups. Also, models will be adjusted for age, sex, race, types of surgery, types of pain, baseline measurement of NRS-11, PHQ-9 and GAD-7. The aim is to study the effect of VR intervention on long-term change of pain intensity.

7.6.2 Secondary Analyses

We will conduct robust standard error estimates linear regression models adjusted for the baseline to find the effects of VR interventions on the changes of depression for both short-term (7 days) and long-term (6 months). Short-term analyses will use time points at baseline and day 5. Long-term analyses will use time points at baseline and month 6. Similarly, we will compare the average change of pre- and post- intervention TRPV1 and TRPA1 collected from blood between groups using robust standard error estimates linear regression models, and also for short-term and long-term analyses. Similarly, use of MME will be analyzed in the same way for short-term (7 days) and long-term (6 months) analyses. In addition, robust standard error estimates linear regression models will be fit to find the effects of VR interventions on LOS and biomarkers collected from CSF. All above models will be adjusted for age, sex, race, types of surgery, types of pain, baseline measurements of NRS-11, PHQ-9 and GAD-7.

7.6.3 Missing data Analyses

In the event that <10% of data is missing, no changes will be performed on the data. The expectation is that no significant changes will result from drop-out of this quantity of missing data. Otherwise, in the event that >10% of the data is missing, more specific models will be used. To determine the type of missing data, graphical exploration will be performed separately for missing completely at random (MCAR), missing at random (MAR) and non-ignorable (NI). If significant overlap of missing and non- missing values is observed, then missing data will be considered MCAR. If missing values and true observations are overlapping, but appear in patterns (i.e. more missing values as for the later observations), then the data will be treated as MAR. In the event that missing and observed values are non-overlapping, then data will be treated as NI. Additional exploratory analysis may be performed to verify the type of missingness. After confirmation, multiple imputations accounting for clustering and “brute-force” pooling of results will be performed.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form(s) contained in Appendix II — and any subsequent modifications — will be reviewed and approved by the University of Washington (UW) IRB with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the UW.

Subsequent to initial review and approval, the IRB will review the protocol at least annually. The Investigators will make safety and progress reports to the IRB and NIH at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

8.2 Informed Consent

Written informed consent will be obtained from each study participant and they will be provided with a copy of their signed informed consent form.

8.3 Risks

There are some foreseeable risks associated with (1) the use of virtual reality (2) blood collection and (3) cerebral spinal fluid extraction.

Virtual reality may cause anxiety in some patients because viewers experience everything as if they were there in the scene. In addition, nausea may become an issue for some patients as realistic simulated motions can affect a person’s perception of time and space leading to dizziness, disorientation, blackouts or possibly seizures. VR headsets can cause severe eye strain among users as patients need to focus on a pixelated screen that uses a single refractive optic element. VR headsets do not usually address the optic issues with near-to-eye devices, and they may become uncomfortable both to the eyes and head. These side effects are not common and will be monitored by study staff.

When performed correctly and according to industry standards, venipuncture complications are rare. However, even when properly performed, complications can

include fainting, dizziness, hematoma, nerve injury, and arterial puncture or laceration. We expect complications from venipuncture to be negligible.

Complications of the optional spinal tap procedure may briefly induce headache, nausea, dizziness and backache. More serious complications of a spinal tap include irritation of a nerve that may lead to temporary numbness or tingling pain in the legs or bleeding into the spinal canal. Infection where the needle was inserted may also occur in rare instances. Since undergoing a spinal tap may cause severe mental and physical discomfort for some patients, this procedure is optional.

Although study staff will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Study staff will be trained in advance to avoid such situations.

8.4 Benefits

There may be direct benefits to participants participating in the REVEAL-Pain Study. Success of the intervention outlined may result in reduction of acute pain post-orthopedic surgery for participants as a result of short-term usage of the VR headset. Additionally, patients may also experience long-term reduction in chronic pain with the regular use of virtual reality technology in the months following their orthopedic surgery. As a result of the reduction in chronic pain, patients may expect to benefit from a significant reduction in the use of opioids to manage their pain symptoms. Due to a reduction in the use of opioids as pain management, patients may be less likely to adopt unhealthy relationships with opioid medication. Similarly, a reduction in chronic pain symptoms may also lead to a reduced incidence in symptoms of depression and anxiety.

In addition, there are significant foreseeable benefits to society as a result of the success of this potential treatment. Non-pharmacological options for pain management have not been well implemented as options for patients who do not wish to consume opioid medication. Proper justification of VR as a means to reduce pain will eventually transform the clinic’s environment to be more accepting of non-pharmacologic options for pain treatment. Larger and wider adoption of this technology will eventually lead to a total change in the milieu of how we as a society view pain. This will instigate health insurance plans to more regularly provide reimbursement for non-pharmacologic pain management interventions, giving patients full jurisdiction over how to manage their pain symptoms.

8.5 Incentives

After discharge of participants from the hospital post-surgery, participants will be provided with a $20 incentive for every follow-up visit they attend and complete study compredures (since CSF is optional, it is not necessary to receive the incentive). A bonus of $100 will be provided if the patient does not withdraw from the study prior to 6 months of participation and completion of all study procedures. These incentives have been designed to be non-coercive.

8.6 Confidentiality

All study-related information will be stored securely in study staff offices at the UW. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by any government and regulatory authorities, and the IRB.

8.7 Communicable Disease Reporting Requirements

While communicable diseases are not expected to be involved, study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities and participants will be made aware of all reporting requirements during the study informed consent process.

8.8 Study Discontinuation

The study also may be discontinued at any time by any government or regulatory authorities, or the IRB.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 UW Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the UWMC Laboratory:

- Blood

The UW lab will perform Chemistry and Hematology tests as indicated in Appendix I.

Assessment of whole blood will be performed with Genome-wide assays of mRNA expression using the SurePrint G3 Human Gene Expression 8×60K v2 Microarray Kit at participating institutions.

- [OPTIONAL] Cerebrospinal Fluid

Assessment Type: Kyneuronic acid will be assessed using an enzyme-linked immunosorbent assay (ELISA) kit at all participating institutions. Other associated metabolites (Quinolinic Acid, Proglutamic Acid, Hydroxymethyglutarate, Ethylmalonic Acid, 5-Hydroxyindoleacetate and Vanilmandelate) will be assessed by High Performance Liquid Chromatography (HPLC) at University of Washington.

We will adhere to standards of good clinical laboratory practice, and standard operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens. Specimen collection, testing, and storage will be documented using an internal study REDCap database.

9.2 Quality Control and Quality Assurance Procedures

The UW clinical lab is certified under the Continuous Laboratory Improvement Act of 1988 (CLIA-certified). Study staff will maintain documentation of certification in the study regulatory binder.

9.3 Specimen Storage and Possible Future Research Testing

Study site staff will store all blood and CSF collected in this study at least through the end of the study. In addition, study participants will be asked to provide written informed consent for both their blood sample and cerebrospinal fluid to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration and Study Activation

Prior to implementation of this protocol, and any subsequent full version amendments, this protocol, informed consent form (ICF), and other study related documents will be approved by the UWMC IRB.

10.2 Study Coordination

This study does not require an IND or IDE (requirement has been waived by UW IRB).

Study implementation will be directed by this protocol. Since this is a single center study, all study materials will be developed by the study team. Data will be recorded and managed via REDCap and the study team will be responsible for data entry, cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the Investigator on a quarterly basis for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team. The Investigator will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management and documentation.

10.3 Study Monitoring

This study will be self-monitored by the study team and may be audited internally by the UW IRB. If audited, monitors may:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

The Investigators will allow monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

10.4 Protocol Compliance

The study will be conducted in full compliance with the protocol.

10.5 Investigator's Records

The study site investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least three years after submission of the manuscript to the Investigator's chosen journal. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened for and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.6 Use of Information and Publications

Publication of the results of this study will be governed by the IP policies of UW. Details can be found on the UW Office of Research website.

11.0 FACILITIES, RESOURCES, AND EQUIPMENT

Laboratory: UWMC has a fully functional clinical laboratory that regularly processes an extremely high load of patient biosamples that is CLIA-certified. Study staff will use this lab to process all research blood and CSF samples following standard protocols. Prior to study initiation, the study team will contact the lab Director to establish sample testing protocols and delivery of test results to study staff while maintaining participant confidentiality. These protocols have been used in previous studies at the lab.

Clinical: UWMC is located at 1959 N.E. Pacific St., Seattle, WA and is a leading center for orthopedics in the US that regularly sees over 100 orthopedic surgery cases per week, providing a sufficient pool from which we can recruit our study participants. UWMC's pain clinic is also a top pain center in the US and has extremely experienced physicians and researchers that will be able to assist with recruitment and collaborate on this trial, if needed.

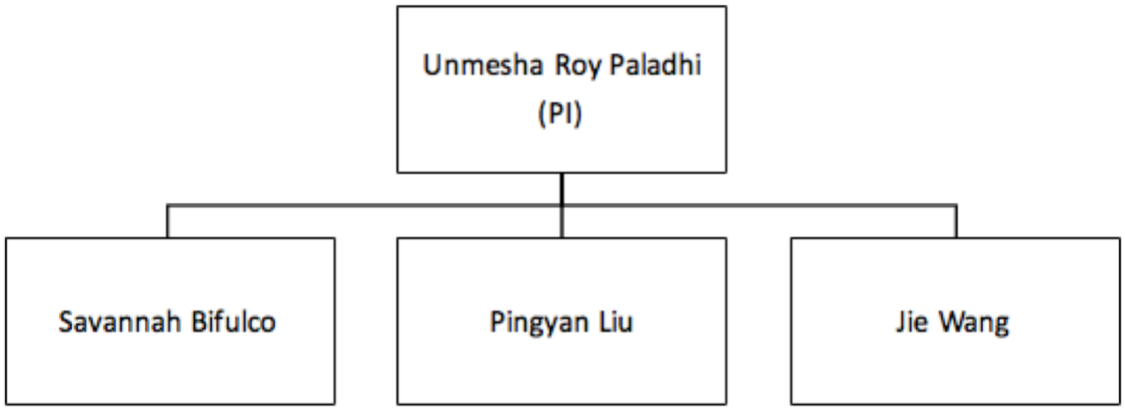
Administrative: All four Investigators in this project have offices near the orthopedic and pain clinics at UWMC. Office space will also be made available to those hired to run the study procedures. They also have access to the University of Washington's library electronic resources and data analysis software such as Stata and R. Information software

such as Zoom and Skype is available for optimal telecommunications across members of the research team.

Other:

- Diversity/collaborative resources: The research team has the largest diversity regarding ethnicity and knowledge compared to other groups. Four members process different academic major backgrounds: Ms. Roy Paladhi is from the Department of Epidemiology, Ms. Bifulco is from the Department of Bioengineering, Ms. Liu is from the Department of Biostatics, and Ms. Wang is from the School of Public Policy and Governance, facilitating the emergence of more innovative insights.
- Consultant: All members in this project are taking *BIOST 524 Design of Medical Studies* this Spring 2020. The instructor of the course, Dr. Thomas Fleming, as well as TA Subodh Selukar have abundant clinical experience and could provide useful instructions on the design, conduct and analysis of the randomized clinical trial.

12.0 ORGANIZATION AND ADMINISTRATION



Our project team is composed of four researchers with multiple divergent research experience, ranging from natural science to social science.

Unmesha Roy Paladhi, MPH is the study PI, and is an Epidemiology doctoral student at the University of Washington and a Graduate Research Assistant at Seattle Children's Hospital. Ms. Roy Paladhi has abundant clinical experience and great interests in exploring the use of new technologies in the context of epidemiological studies in multiple fields, especially pediatric chronic pain. Previously, she was a Clinical Research

Coordinator in the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania's Perelman School of Medicine.

Savannah Bifulco is a doctoral student in the Department of Bioengineering, with a focus on developing patient-specific electrophysiological cardiac models. She has close collaborations with the cardiac electrophysiology clinicians at University of Washington Medical Campus. Savannah also has abundant clinical experiences and has got Good Clinical Practice in the Collaborative Institutional Training Initiative (CITI Program).

Pingyan Liu is a first-year Masters student in Biostatistics and has a solid knowledge foundation of statistics. She has rich experience regarding data analysis in R and random trial design, including building regression models, data analysis and interpreting results in a scientific way to both biostatisticians and non-biostatisticians.

Jie Wang is a Masters student in Public Policy and Governance at the University of Washington and will pursue her doctoral studies at the University of California, Irvine this fall. Equipped with a background of social science, Ms. Wang could provide knowledge in terms of how to form a fair relationship with patients, how to win trust from patients, and how to develop policies based on our clinical findings.

13.0 REFERENCES

1. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393(10180):1537-1546. doi:10.1016/S0140-6736(19)30352-6
2. Naseem Ahmadpour, Hayden Randall, Harsham Choksi, Antony Gao, Christopher Vaughan, Philip Poronnik, Virtual Reality interventions for acute and chronic pain management, The International Journal of Biochemistry & Cell Biology, Volume 114, 2019, 105568, ISSN 1357-2725.
3. Manivannan S, Al-Amri M, Postans M, Westacott LJ, Gray W, Zaben M. The Effectiveness of Virtual Reality Interventions for Improvement of Neurocognitive Performance After Traumatic Brain Injury: A Systematic Review. J Head Trauma Rehabil. 2019;34(2):E52-E65. doi:10.1097/HTR.0000000000000412
4. Game-Based Virtual Reality Interventions to Improve Upper Limb Motor Function and Quality of Life After Stroke: Systematic Review and Meta-analysis Pablo Domínguez-Téllez, Jose A. Moral-Muñoz, Alejandro Salazar, Esteban Casado-Fernández, and David Lucena-Antón Games for Health Journal 2020 9:1, 1-10
5. Ghoneim MM, O'Hara MW. Depression and postoperative complications: an overview. BMC Surg. 2016;16:5. Published 2016 Feb 2. doi:10.1186/s12893-016-0120-y
6. Pagé MG, Watt-Watson J, Choinière M. Do depression and anxiety profiles over time predict persistent post-surgical pain? A study in cardiac surgery patients. Eur J Pain. 2017;21(6):965-976.
7. Spiegel B, Fuller G, Lopez M, Dupuy T, Noah B, Howard A, Albert M, Tashjian V, Lam R, Ahn J, Dailey F. Virtual reality for management of pain in hospitalized patients: A randomized comparative effectiveness trial. PloS one. 2019;14(8)
8. Frey DP, Bauer ME, Bell CL, et al. Virtual Reality Analgesia in Labor: The VRAIL Pilot Study-A Preliminary Randomized Controlled Trial Suggesting Benefit of Immersive Virtual Reality Analgesia in Unmedicated Laboring Women. Anesth Analg. 2019;128(6):e93-e96.
9. Chirico A, Yaden DB, Riva G, Gaggioli A. The potential of virtual reality for the investigation of awe. Frontiers in psychology. 2016 Nov 9;7:1766.
10. Erlenwein J, Müller M, Falla D, Przemeck M, Pfingsten M, Budde S, Quintel M, Petzke F. Clinical relevance of persistent postoperative pain after total hip replacement–a prospective observational cohort study. Journal of pain research. 2017;10:2183. https://doi.org/10.2147/JPR.S137892
11. Macrae WA, Davies HTO. Chronic postsurgical pain. In: Crombie IK. ed. Epidemiology of pain. Seattle: IASP Press; 1999:125–42.
12. Bruce J, Quinlan J. Chronic Post Surgical Pain. Rev Pain. 2011;5(3):23-29. doi:10.1177/204946371100500306
13. H. J. Gerbershagen, J. Rothaug, C. J. Kalkman, W. Meissner, Determination of moderate-to-severe postoperative pain on the numeric rating scale: a cut-off point analysis applying four different methods, BJA: British Journal of Anaesthesia, Volume 107, Issue 4, October 2011, Pages 619–626, https://doi.org/10.1093/bja/aer195
14. Calvo M, Dawes JM, Bennett DL. The role of the immune system in the generation of neuropathic pain. Lancet Neurol. 2012;11:629–42.
15. Bertin S, Raz E. Transient receptor potential (TRP) channels in T cells. InSeminars in immunopathology 2016 May 1 (Vol. 38, No. 3, pp. 309-319). Springer Berlin Heidelberg.

16. Iacob E, Light KC, Tadler SC, Weeks HR, White AT, Hughen RW, et al. Dysregulation of leukocyte gene expression in women with medication-refractory depression versus healthy non-depressed controls. BMC Psychiatry. 2013;13:273
17. Gerbershagen HJ, Rothaug J, Kalkman CJ, Meissner W. Determination of moderate-to-severe postoperative pain on the numeric rating scale: a cut-off point analysis applying four different methods. Br J Anaesth. 2011;107(4):619-626.

4.0 APPENDICES

I BUDGET

	Year 1 (09/01/2020 - 08/30/2021)	Year 2 (09/01/2021 - 08/30/2022)	Year 3 (09/01/2022 - 08/30/2023)	Year 4 (09/01/2023 - 08/30/2024)	Year 5 (09/01/2024 - 08/30/2025)
Scientists and senior personnel					
PI (50% effort)	$ 60,000	$ 60,000	$ 60,000	$ 60,000	$ 60,000
Salary	$ 50,400	$ 50,400	$ 50,400	$ 50,400	$ 50,400
Fringe (16%)	$ 9,600	$ 9,600	$ 9,600	$ 9,600	$ 9,600
Other personnel					
1. Co-Investigator (10% effort)	$ 10,000	$ 10,000	$ 10,000	$ 10,000	$ 10,000
Salary	$ 8,400	$ 8,400	$ 8,400	$ 8,400	$ 8,400
Fringe (16%)	$ 1,600	$ 1,600	$ 1,600	$ 1,600	$ 1,600
2. Co-Investigator (10% effort)	$ 10,000	$ 10,000	$ 10,000	$ 10,000	$ 10,000
Salary	$ 8,400	$ 8,400	$ 8,400	$ 8,400	$ 8,400
Fringe (16%)	$ 1,600	$ 1,600	$ 1,600	$ 1,600	$ 1,600
3. Co-Investigator (10% effort)	$ 10,000	$ 10,000	$ 10,000	$ 10,000	$ 10,000
Salary	$ 8,400	$ 8,400	$ 8,400	$ 8,400	$ 8,400
Fringe (16%)	$ 1,600	$ 1,600	$ 1,600	$ 1,600	$ 1,600
4. Clinical Research Coordinator (100% effort)	$ 60,000	$ 60,000	$ 60,000	$ 0	$ 0
Salary	$ 50,400	$ 50,400	$ 50,400	$ 0	$ 0
Fringe (16%)	$ 9,600	$ 9,600	$ 9,600	$ 0	$ 0
Equipment purchase	$ 23,407	$ 0	$ 0	$ 0	$ 0
1. The Oculus Rift Virtual Reality ($399/	$ 3,192	$ 0	$ 0	$ 0	$ 0

piece, 8 sets)					
2. Samsung Galaxy S6 ($380/piece, 8 sets)	$ 3,040	$ 0	$ 0	$ 0	$ 0
3. Medical Lumbar Puncture Needles	$ 1,200	$ 0	$ 0	$ 0	$ 0
4. Kynurenic Acid Kit	$ 15,975	$ 0	$ 0	$ 0	$ 0
Office Supplies	$ 3,000	$ 3,000	$ 3,000	$ 3,000	$ 3,000
Conference Costs (domestic only)	$ 7,000	$ 7,000	$ 7,000	$ 7,000	$ 7,000
Travel	$ 6,000	$ 6,000	$ 6,000	$ 6,000	$ 6,000
Registration	$ 1,000	$ 1,000	$ 1,000	$ 1,000	$ 1,000
Publication Costs	$ 0	$ 0	$ 0	$ 0	$ 5,000
Other Direct Costs	$ 12,480	$ 12,480	$ 12,480	$ 5,000	$ 5,000
1. Compensation to Participants ($220/participant)	$ 7,480	$ 7,480	$ 7,480	$ 0	$ 0
2. Other	$ 5,000	$ 5,000	$ 5,000	$ 5,000	$ 5,000
Overhead (50% of salaries)	$ 75,000	$ 75,000	$ 75,000	$ 45,000	$ 45,000
Total cost per year	$ 263,887	$ 240,480	$ 240,480	$ 143,000	$ 148,000
TOTAL REQUESTED AMOUNT					**$ 1,035,847**

II SAMPLE INFORMED CONSENT FORM

UNIVERSITY OF WASHINGTON
The Role of a Virtual Reality Intervention on Postoperative Pain
(REVEAL-Pain Study)
INFORMED CONSENT FORM

Principal Investigator: Unmesha Roy Paladhi, MPH

STUDY TEAM:

Team member	Role	Contact Information
Unmesha Roy Paladhi, MPH	Principal Investigator (PI)	uroy@uw.edu
Savannah Bifulco, BS	Co-PI	sbifulco@uw.edu
Pinyan Liu	Co-PI	pliu5@uw.edu
Jie Wang	Co-PI	jwang18@uw.edu

24 hour Emergency Contact Number: (206)-987-2000 and ask for the orthopedic resident on call

If you have questions about your rights as a research study participant, you can call the University of Washington Medical Center (UWMC) Institutional Review Board (IRB) at (206)-987-2000.

1. Researcher's Statement:
You have the option to take part in a research study. The goals of this form are to give you information about what would happen in the study if you choose to take part and to help you decide if you want to be in the study.

Feel free to take notes, write questions, or highlight any part of this form, and ask us any questions you may have as we review this with you.

2. What you should know about this study:
This form explains what would happen if you join this research study.

- Please read it carefully. Take as much time as you need.
- Please ask the research team questions about anything that is not clear.
- You can ask questions about the study any time.
- If you choose not to be in the study, it will not affect your care at University of Washington Medical Campus.
- If you say 'Yes' now, you can still change your mind later. You can quit the study at any time.
- You would not lose benefits or be penalized if you decide not to take part in the study or to quit the study later

3. What is the goal of this study?
The goal of any research study is to answer questions. We (the research team listed on the front of this form and our staff) are doing this research study to answer three main questions:

- Does the use of a Virtual Reality (VR) intervention after orthopedic surgery reduce the incidence of acute and chronic pain?
- If so, does it also have any effects on depression and anxiety?
- Does the use of a VR intervention reduce the usage of opiates for the treatment of chronic pain?
- Does the use of a VR intervention affect feelings of acute pain postoperative?

4. Why do I have the option of joining this study?
You have the option to take part in this research study because you will be undergoing one of the following five (5) orthopedic procedures:
(1) Arthroscopy
(2) Soft tissue repair
(3) Joint replacement
(4) Bone fracture repair
(5) Osteotomy

5. How many people will take part in this study?

We will include up to 100 people in this study, to ensure we have 80 people finish all study procedures.

6. If I agree to join this study what would I need to do?

If you join the study, you will have to either use a VR intervention or use a health and wellness web-based TV channel after your orthopedic surgery. In order to see the effect these interventions may have on your recovery, we will also ask you to complete a few questionnaires and provide us with some blood samples. Additionally, if you consent to this extra part, we will conduct a lumbar puncture (spinal tap) to obtain some cerebrospinal fluid. Your participation would start today where you complete some forms and last for 6 months after you have your surgery.

While most visits would be in-person, some follow-up visits after your surgery can be conducted remotely, over the phone. Below is a table describing exactly what your participation would entail:

Visit #	Visit Description	Visit Procedures
1	Consent and Enrollment Visit	- Informed consent process - (If possible) Complete screening questionnaire
2	Enrollment and (Pre-)Surgery Visit	- Complete Baseline Questionnaire
3	Post-Surgery In-patient Visit (Days 0-5)	- Day 0: Receive your intervention, provide blood and (optional) CSF - Days 1-5: Complete NRS-11 questionnaire, maintain intervention diary, and provide blood - Days 1 & 5: Complete PHQ-9 and GAD-7 questionnaires - Days 2 & 5: Provide CSF (optional)
4	1 Month Follow-up	- Complete study questionnaire and show study staff intervention diary - Provide blood sample - Return study equipment
5	2 Month Follow-up	- Complete study questionnaire and show study staff intervention diary - Provide blood sample and (optional) CSF
6	3 Month Follow-up	This visit can be conducted remotely via phone by study staff or in-person if participant has a scheduled clinic follow-up. If remotely conducted, blood won't be collected.

		- Complete study questionnaire and show study staff intervention diary - Provide blood sample
7	4 Month Follow-up	- Complete study questionnaire and show study staff intervention diary - Provide blood sample and (optional) CSF
8	5 Month Follow-up	This visit can be conducted remotely via phone by study staff or in-person if participant has a scheduled clinic follow-up. If remotely conducted, blood won't be collected. - Complete study questionnaire and show study staff intervention diary - Provide blood sample
9*	6 Month Follow-up	- Complete study questionnaire and show study staff intervention diary - Provide blood sample and (optional) CSF - Do exit interview

*this visit will still have to be completed if you choose to withdraw at any time prior to this visit.

7. How long will I be in this study?

If you chose to take part in all the study visits, you would be in the study for 6 months.

If you join the study, you can decide to stop at any time for any reason. If you decide to stop, please contact Ms. Roy Paladhi so you can leave the study safely.

The research study Investigators could also decide to take you out of this study. This might happen if we find out that it is not safe for you to stay in the study. Or it might happen if you cannot come to enough of the study visits.

8. What are the potential harms or risks if I join this study.

Possible side effects of VR therapy:

- Discomfort
- Loss of Spatial Awareness
- Dizziness and Disorientation
- Eye Soreness
- Eye or muscle twitching
- Nausea
- Blackouts
- Seizures

Possible side effects of CSF procedure:

- Headache
- Backache
- Nausea and vomiting
- Dizziness
- Irritation of a nerve may cause temporary numbness, tingling or pain down your legs
- Infection where the needle was inserted
- Bleeding into the spinal canal

Possible side effects of venipuncture (blood draws):

- Fainting
- Dizziness
- Hematoma
- Nerve injury
- Arterial puncture or laceration

As this research study involves an experimental intervention, we do not know all of the possible harms or risks. If you take part, we would tell you about any new information we learn that might affect your health or your willingness to stay in the study.

9. What are the potential benefits of this study?

Potential Benefits for you

Being in this study might benefit you in the following ways:

- Chronic pain results from orthopedic surgery may be reduced
- Acute pain from orthopedic surgery may be reduced
- Your opiate usage post-surgery may be reduced
- Possible depression or anxiety symptoms as a result of your surgery may reduce

Potential Benefits for others

We hope to use the information we get from this study to benefit others undergoing orthopedic surgery as well as others in need of non opioid or non-pharmacologic treatment options for chronic or acute pain.

10. What other options do I have?

If you chose not to be in this study, you can:
Undergo your scheduled orthopedic surgery without any non-clinical post-operational intervention.

Please further discuss this with the research team or your orthopedic surgery provider.

11. How would you keep my information confidential?

If you take part, we will make every effort to keep your information confidential.

We will store all of your research records in locked cabinets and secure computer files .We will not put your name on any research data. Instead we will label your information with a unique study number. The master list that links your name to your study number will be stored in a locked cabinet or on a secure computer file.

If the results of this research are published, we would not use information that identifies you.

We would only use your information for research. These are some reasons that we may need to share the information you give us with others:

- If it's required by law.
- If we think, you or someone else could be harmed.

Sponsors, government agencies, or research staff sometimes look at forms like this and other study records. They do this to make sure the research is done safely and legally. Anyone who reviews study records would keep your information confidential.

- Agencies or sponsors that may look at study records include:
- The US Food and Drug Administration (FDA)
- Hospital Auditors, Government Agencies
- Others responsible for watching over the safety, effectiveness, and conduct of the research

If you join this study, we would put information about this study in your medical record. We do this because the research study involves patient care. We will also keep your results until 2026.

12. Will it cost me money to be in the study?

If you take part in this study, there would be no additional cost to you or your insurance company, other than those typically incurred as part of your clinically scheduled surgical procedure and recovery.

13. What if I were injured because I joined the study?

If you were injured as the direct result of this research study, UWMC would provide treatment. We would refer you for treatment if needed. You would NOT need to pay for this treatment and neither would your insurance company. This is the only compensation offered for study-related injuries. It is important that you tell the Principal Researcher, Ms. Roy Paladhi, if you think that you have been injured because of taking part in this study. You can contact her at uroy@uw.edu.

14. Would I be paid if I join this study?

You may receive $20 for every follow-up visit you attend and complete all study procedures. Since there are 6 follow-up visits, you may receive up to $120. If you attend all 6 follow-up visits, you will receive a $100 bonus incentive for a total of $220.

15. Who do I contact if I have problems, questions, or want more information?

If I have questions or would like to know about...	You can contact ...	At …
• Emergencies • General Study Questions • Research related injuries • Any research concerns or complains	Unmesha Roy Paladhi Pinyan Liu Jie Wang Savannah Bifulco	Email: uroy@uw.edu Email: pliu5@uw.edu Email: jwang18@uw.edu Email: sbifulco@uw.edu
Your rights as a research participant	Institutional Review Board. This is a group of scientists and community members who make sure research meets legal and ethical standards.	Phone: (206) 987-7804

More Information: A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search for this website at any time before or after the trials completion.

16. If I join the study, can I stop?

Yes. Taking part in research is always your decision. If you decide to be in the study, you can change your mind at any time. We ask that you please tell Ms. Roy Paladhi, the primary investigator of this research. You can reach her at the aforementioned email address.

If you choose to leave this study, it will not affect your care at UWMC in any way. You will not lose any benefits or be penalized if you choose to leave this study.

17. What would my signature on this form mean?

Your signature would mean:

- The research study was explained to you
- You had a chance to ask all the questions you have at this time. All your questions have been answered in a way that is clear.
- You understand that the persons listed on this form will answer any other questions you may have about the study or your rights as a research study participant.
- You have rights as a research participant. We will tell you about new information or changes to the study that may affect your health or your willingness to stay in the study.
- By signing this consent form, you do not give up your legal rights. The researcher(s) or sponsor(s) are not relieved of any liability they may have.
    - You agree to take part in the research study

_____

Printed name of participant

_____

Signature of research participant

_____ _____

Date Time

18. Witness Statement

I have been present during the verbal presentation of this research study.

_____

Printed Name of Witness

_____

Signature of Witness

_____

Date Time

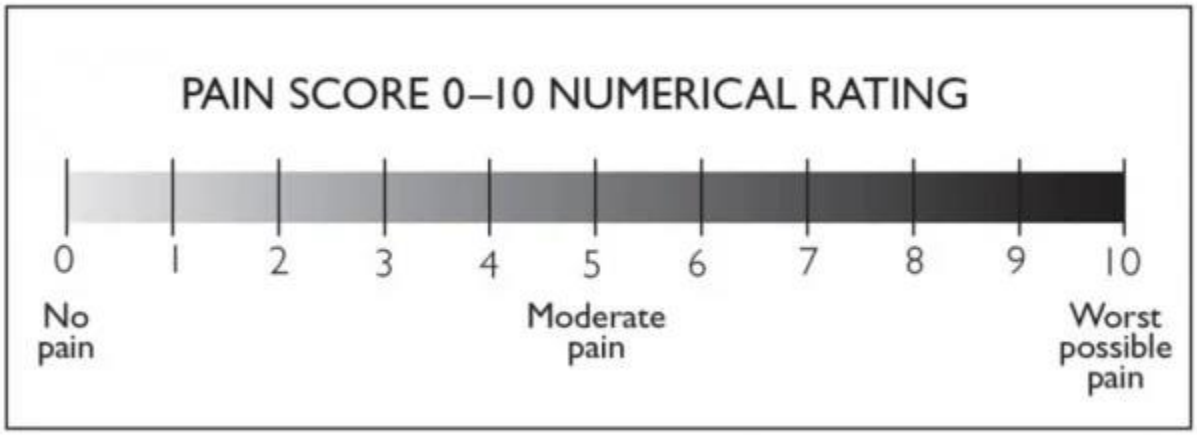
III SAMPLE DATA COLLECTION FORM

Baseline (Visit 2) Questionnaire and Source Document

PID# _____

Date _____

1. Looking at the below scale, please circle the number that matches most closely your pain intensity at the current moment:



2. Please complete the below questions that asks about how you have been feeling over the past 2 weeks:

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ **DATE:**_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

3. Same as the previous question, please answer the below questions regarding how you have been feeling over the past 2 weeks:

GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

4. Please inform study staff if you are taking any medications (prescription or over the counter) currently.

Thank you for answering these questions. Please hand this form back to the study staff now.

FOR STUDY STAFF USE ONLY:

Date of scheduled orthopedic surgery: _____

Type of orthopedic surgery:

___ Arthroscopy

___ Soft tissue repair

___ Joint replacement

___ Bone fracture repair

___ Osteotomy

Type of Pain:

___ Nociceptive (Joint/Bone/Soft tissues)

___ Neuropathic

___ Mixed

Location of surgery: _____

History of Pain (unrelated to surgery):

Frequency of Pain: → EXCLUDE IF THEY SELF-REPORT CHRONIC PAIN CONDITION

___ Constant

___ Frequent

___ Infrequent

___ Unknown

Pregnancy Confirmation:

___ Pregnant → EXCLUDE IF THEY SELF-REPORT PREGNANCY

___ Not pregnant