CAN A VIRTUAL REALITY MODALITY SUBSTITUTE FOR PROCEDURAL SEDATION AND IMPROVE TOLERANCE IN PATIENTS RECEIVING EPIDURAL STEROID INJECTIONS FOR PAIN? A RANDOMIZED CONTROLLED TRIAL.

Protocol Number: IRB00255275

National Clinical Trial (NCT) Identified Number: NCT04887285

Principal Investigator: Steven P. Cohen, MD

Funded by: Department of Defense (DoD) Defense Health Agency (DHA) through the Uniformed Services University (USU)

Grant Number: HU00011920011

Version Number: 5.0

06 Dec 2022

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

Table of Contents

STATEMENT OF COMPLIANCE

(1) The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name*: Steven P. Cohen, MD

Title*: Chief of Pain Medicine, Professor of Anesthesiology and Critical Care Medicine, Neurology and Physical Medicine & Rehabilitation

Investigator Contact Information
Affiliation*: Johns Hopkins Department of Anesthesiology and Critical Care Medicine, Division of Pain Medicine
Address: 601 N Caroline St. #3062 Baltimore, MD 21287
Telephone: (410) 955-7246
Email: scohen40@jhmi.edu

Signed: _____ _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

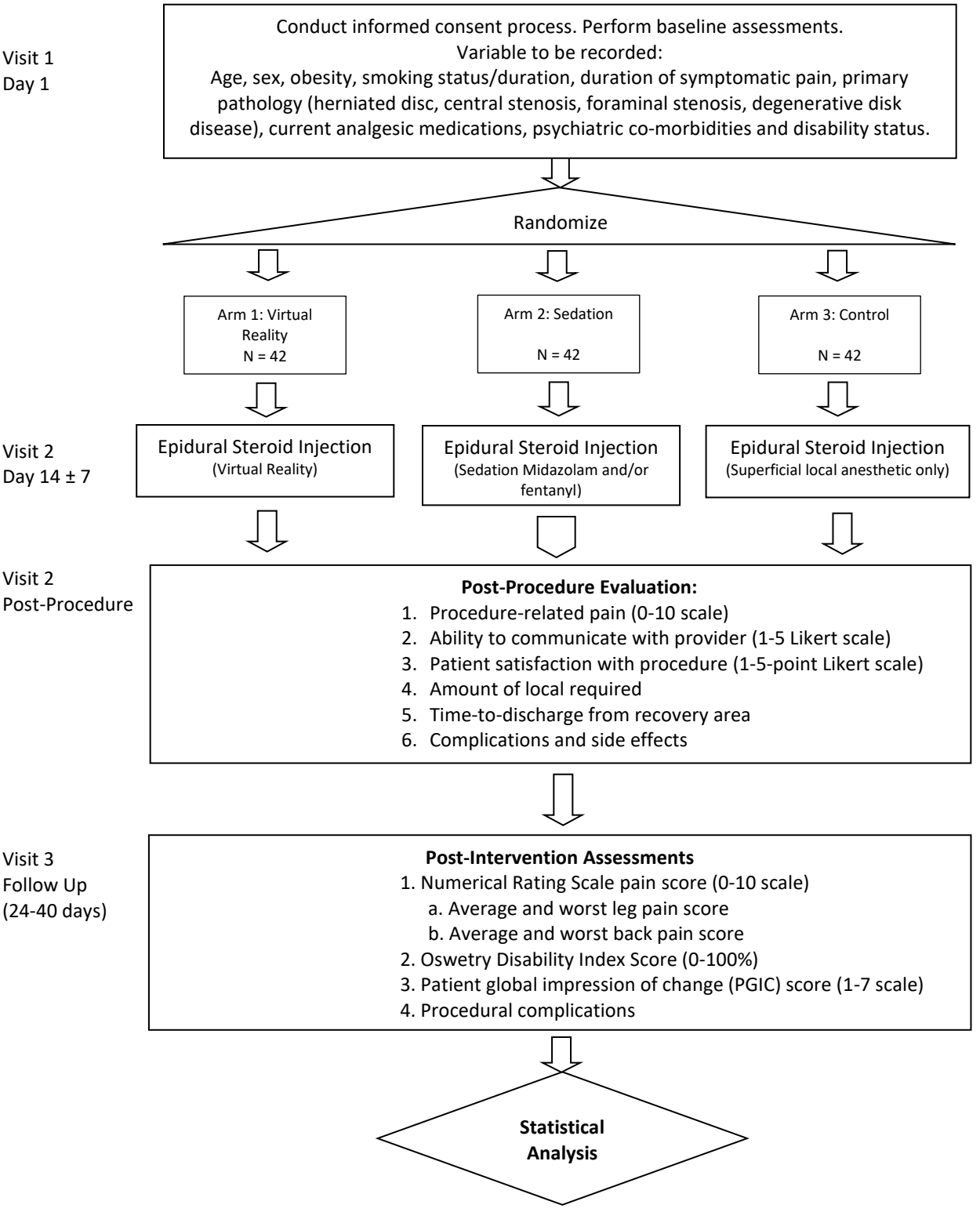
Title:	Can distraction substitute for procedural sedation and improve tolerance in patients receiving lumbar epidural steroid injections (ESI) for pain? A randomized controlled trial.
Study Description:	This study examines the impact of virtual reality compared to sedation (midazolam and/or fentanyl) and no intervention on pain experienced from an ESI. The intervention group (who receive virtual reality as a distraction modality) is compared to a sedation group and a control group.
Objectives*:	**Aim 1:** To determine the relative efficacy of virtual reality as a distraction modality compared to a sedation group for procedure-related pain, procedural satisfaction, and 1-month pain and functional outcomes. **Aim 2:** To determine the relative efficacy of virtual reality as a distraction modality compared to a control group for procedure-related pain, procedural satisfaction, and 1-month pain and functional outcomes. **Aim 3:** To determine whether demographic and clinical characteristics are associated with outcome measures (personalized medicine). **Aim 4:** To explore whether virtual reality and lower procedure-related pain scores affect 1-month outcomes.

Endpoints*:	Primary Endpoint: Procedure-related pain in 0-10 verbal rating scale (VRS) Secondary Endpoints: Procedure-related satisfaction on 1-5 Likert scale (5=most satisfied, 1= least satisfied), amount of superficial local anesthetic used, EEG-derived parameters (change from baseline in spectral edge frequency during procedure), time-to-discharge from recovery area, mean reduction in 0-10 numerical rating scale (NRS) pain scores for average and worst leg pain at 1-month, mean reduction in NRS pain scores for average and worst back pain at 1-month, patient ability to communicate with provider on a 1-5 Likert scale, mean reduction in Oswestry disability index (41) score (0-100%) at 1-month, patient global impression of change (PGIC) (42) at 1-month, adverse events and complications. A 1-month successful outcome will be categorically defined as a 2-point or greater decrease in average leg pain score coupled with a score of $\geq$ 5/7 on the PGIC (42).
Study Population:	Patients undergoing ESI will be eligible for inclusion in the study and will be sub-allocated based on the type of injection (transformainal vs. interlaminar). Inclusion criteria will include radicular low back pain, baseline average leg pain score of $\geq$ 4/10, MRI findings consistent with symptoms, duration of pain > 6 weeks, and no previous lumbar spine surgery. Excluded from participation will be individuals with non-concordant MRI findings, previous ESI within the past 6 months, secondary gain expected to influence treatment outcomes, poorly controlled psychiatric condition that could affect outcome (e.g. active substance abuse) or impose a barrier to participation (e.g. anxiety disorder requiring sedation), morbid obesity (> 40 BMI), and anticoagulation therapy that cannot be stopped and could warrant a different treatment approach (e.g. caudal injection with a small-gauge needle).
Phase* or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	This project is a multicenter trial to take place at The Johns Hopkins Blaustein Pain Treatment Center.

Description of Study Intervention/Experimental Manipulation:	All patients enrolled in the study will already be undergoing lumbar epidural steroid injections for lumbar radicular pain as part of their clinical care. The epidural approach will either be transforaminal or interlaminar depending on clinical judgment (i.e. transforaminal ESI for unilateral pain, interlaminar ESI for bilateral pain). The study will consist of 3 groups: virtual reality, sedation, and a control group which receives no intervention (i.e. standard of care). The virtual reality will receive virtual reality via a headset that consists of a menu of 6 programs that the subject can choice; the sedation group will receive from 1-5 mg of midazolam and up to 150 mcg of fentanyl as clinically indicated, and the control group will not receive an intervention (standard of care). All subjects will also receive 1% lidocaine local anesthetic through a 25-gauge needle for superficial anesthesia, which is standard of care. Subjects will be randomized to each of these groups, with sub-allocation being done stratified by the type of ESI (transforaminal vs. interlaminar).
Study Duration*:	February 28 2022 to February 28, 2024 (24 months in total)
Participant Duration:	1-2 months (window period of 24-40 days)

1.2 SCHEMA

Total N: 126
Pre-screen potential participants by inclusion and exclusion criteria; schedule Visit 1.


Pre-Screening:
Day -30 to
Day 1
Visit 1
Day 1
Conduct informed consent process. Perform baseline assessments.
Variable to be recorded:
Age, sex, obesity, smoking status/duration, duration of symptomatic pain, primary pathology (herniated disc, central stenosis, foraminal stenosis, degenerative disk disease), current analgesic medications, psychiatric co-morbidities and disability status.
Randomize
Arm 1: Virtual Reality
N = 42
Arm 2: Sedation
N = 42
Arm 3: Control
N = 42
Visit 2
Day 14 ± 7
Epidural Steroid Injection
(Virtual Reality)
Epidural Steroid Injection
(Sedation Midazolam and/or fentanyl)
Epidural Steroid Injection
(Superficial local anesthetic only)
Visit 2
Post-Procedure
Post-Procedure Evaluation:
1. Procedure-related pain (0-10 scale)
2. Ability to communicate with provider (1-5 Likert scale)
3. Patient satisfaction with procedure (1-5-point Likert scale)
4. Amount of local required
5. Time-to-discharge from recovery area
6. Complications and side effects
Visit 3
Follow Up
(24-40 days)
Post-Intervention Assessments
1. Numerical Rating Scale pain score (0-10 scale)
a. Average and worst leg pain score
b. Average and worst back pain score
2. Oswetry Disability Index Score (0-100%)
3. Patient global impression of change (PGIC) score (1-7 scale)
4. Procedural complications
Statistical Analysis

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening Day -30 to day 1	Visit 1 Day 1	Visit 2 Day 14 ±7	Visit 2 Post-Procedure	Visit 3 Follow Up Day 24 to 40
EMR Review Eligibility	X				
Informed Consent			X		
Demographics			X		
Clinical history			X		x
Height & Weight			X		x
Randomization			X		
Study Intervention					
Epidural Steroid Injection			X		
Post-Procedure Evaluation					
Procedure related pain (0-10 scale)				X	
Skin wheal pain score (0-10 scale)					
5-point Likert procedure anxiety scale				X	
5-point Likert procedure communication scale				X	
5-point Likert procedure satisfaction scale				X	
Amount of local anesthetic required				X	
Time to discharge from recover area				X	
Complications and side effects				X	
Post-Intervention Assessments					
Numerical Rating Scale (0-10 point) : - Average and worst leg pain score					x
Numerical Rating Scale (0-10 point) : - Average and worst back pain score					x
Oswestry Disability Index Score					x
Patient global impression of change score (1-7 scale)					x
Procedural Complications					x

2 INTRODUCTION

2.1 STUDY RATIONALE

The usage of epidural steroid injections (ESI) underwent dramatic growth between 2000 and 2016. (1) Although their usage has leveled off since that time, they remain one of the most utilized procedures in interventional pain management. (2)

There has also been a commensurate rise in the cost per injection, which has led to increased scrutiny of utilization and outcomes.(3) Many patients receive a bill for anesthesia services or sedation, which increases both risks and costs.(4) This is despite Spine Intervention Society (SIS) and American Society of Anesthesiologists (ASA) recommendations that sedation is not routinely required for basic procedures such as ESI and facet blocks. (5, 6)

The cost of procedural suites and ORs ranges from $10 to $100 per minute of use, depending on the facility and geographic location. This equates to almost 1/3rd of healthcare spending.(7) The use of sedation during pain interventions further increases the overall procedural costs by up to 50% (8) due to added medications, the need for adequate recovery areas, and the need for extended nursing/physician monitoring during and after the procedure. When anesthesiologists are used instead of nurses, as is often the case, the costs dramatically increase. Additionally, sedation increases the complication rate (4) while conferring no benefit for patient satisfaction or outcomes at 1-month.(9) For procedures with diagnostic utility such as facet blocks and sacroiliac joint injections, sedation may increase the false-positive rate, leading to even more unnecessary interventions (i.e. radiofrequency ablation, sacroiliac joint fusions).(9)

There is increasing evidence in the literature that distraction modalities can lead to a decrease in pain, anxiety levels, need for sedative medications, and patient dissatisfaction during painful procedures.(10) These modalities include music,(11) guided meditation(12) and immersive virtual reality.(10) There are no large, randomized control trials testing the comparative-effectiveness of distraction modalities; however, data from several smaller studies is promising. One of the most highly publicized pain articles published in 2019 compared music to midazolam before preoperative peripheral nerve blocks, finding midazolam superior on some metrics (e.g. procedure satisfaction, communication between patient and provider), but equivalent to music on others (anxiety).(13) Yet, the differences in populations (chronic pain patient vs. surgical candidate), purpose (pain-alleviating procedure vs. anesthetic technique) and long-term goals (intermediate or long-term pain relief vs. comfort in the perioperative period) preclude generalization. Our study aims to compare virtual reality as a distraction technique to sedation and a control (standard of care group) in patients with radiculopathy undergoing ESIs, and evaluates their impact on procedural pain, satisfaction, and short-term pain and functional outcomes.

2.2 BACKGROUND

Interventional pain therapy is used to refer to a multitude of different procedures used to treat various chronic pain disorders. Epidural steroid injections (ESI) are one of the most commonly used procedures to

treat radicular pain of various etiologies. To date, there remains significant uncertainty and disagreement regarding the safety of performing these injections using procedural sedation.

Procedural sedation (PS) uses various medication combinations to reduce pain, anxiety and/or motion. These sedative, hypnotic, analgesia or anxiolytic medications are administered to patients in order to improve patient comfort, facilitate amnesia or decrease awareness in patients undergoing diagnostic or therapeutic procedures. (14) PS is administered worldwide to a diverse group of patients and in a variety of clinical settings both in and outside of the operating room. In a study performed by Cucuzella et al, 17% of patients requested sedation before their initial ESI or facet block, with 28% stating they would ask for it before a repeat block. (15)

The American Society of Anesthesiologists specialty guidelines state ESIs do not routinely require procedural sedation.(6) Despite these guidelines, it has been estimated that 53% cervical ESI and 46% of lumbar ESI's are being performed with the use of IV sedation.(16) Supporters of sedation argue that it can decrease the risk of neural injury by facilitating immobility and reduce sudden movement during key portions of the procedure. It can also diminish anxiety, permitting treatment in a population that might not otherwise receive treatment. (17) Chronic pain patients display higher rates of co-morbid psychiatric conditions than the general population. (18) Anxiety disorders have been shown to have a prevalence as high as 35% in chronic pain patients compared to 18% in the general population (19) and in one study 58% of these patients chose to be sedated when it is offered prior to undergoing an ESI. (15) Opponents of sedation argue that safety is improved when patients are responsive because they are better able to provide feedback, thereby reducing the chance of neurological injury. (20) This is supported by ASA's closed claims data that demonstrates 67% of spinal cord injuries occurred in sedated patients undergoing cervical ESIs compared to 19% in non-sedated patients. (4) In the multispecialty working group guidelines on the safe use of ESI, the 13 participating organizations were unanimous in not recommending moderate or deep sedation.(21) In the international guideline committee on the performance of facet interventions chaired by Dr. Cohen, the 14 participating organizations, including the U.S. Depts. of Defense and Veterans Affairs, were unanimous in discouraging the use of sedation for facet blocks.(22)

A variety of cognitive distraction techniques have been described in the literature to reduce pain and anxiety during painful medical procedures. Although there have not yet been any large randomized control trials addressing this question, smaller studies have shown benefit. One study evaluating the effect of music therapy on postoperative pain demonstrated statically significant reduction in pain scores and a decrease in opioid requirements,(23) and other studies have also shown significant reductions in anxiety. Studies have also demonstrated a reduction in pain and anxiety during painful procedures using distraction techniques without compromising provider patient communication.(12)

Immersive virtual reality (VR) has become a promising novel approach to cognitive distraction by virtue of its ability to provide a customized patient-specific illusion through a computer-generated environment. VR enables patients to immerse themselves in an alternative, comfortable environment, combining sensory input from auditory and visual inputs through a head-mounted display, which functions to block unpleasant sensory input from the real world. It has been reported that VR can provide 30%-50% reduction in subjective pain scores (24, 25) and significant reduction in pain-related brain activity in response to an acute painful stimulus using fMRI.(10) This is an excellent model for evaluating the

reduction of procedure-related pain during ESI. Collectively, these findings suggest that non-pharmacologic modalities such as immersive virtual reality can be used as a replacement for procedural sedation in patients with and without high anxiety levels undergoing ESI, thus improving safety.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

All patients will already be receiving ESI, so participation in the study will confer no additional procedure risks. Sedation is used in between 40% and 50% of lumbar ESI in the U.S., and typically employs midazolam (an anxiolytic) and fentanyl (a short-acting opioid). Although some patients in our study may receive both opioids and benzodiazepines, which could have additive effects, these medications will be given in low doses (i.e. the patients will remain responsive to verbal stimuli, and will be monitored by anesthesiologists and nurses.(16) In the clinical studies that have evaluated sedation during ESI and other procedures including one performed at Johns Hopkins and Walter Reed, there have been no serious side effects associated with sedation.(9) At Johns Hopkins and Walter Reed, there have been no reported adverse events related to light sedation during ESI in the past 15 years. The use of VR is now used at Johns Hopkins in anxious individuals undergoing ESI and other procedures, and there have been no serious adverse events reported in any trials evaluating its use for acute pain.

Epidural Steroid Injections:

ESI are associated with a number of minor complications that do not involve permanent impairment. These risks include vasovagal reactions, headache, unintentional dural puncture and exacerbation of pain. There is also concern of rare but catastrophic injuries to the central nervous system, which includes stroke, spinal cord injury that could result in increased pain, severe permanent disability or death (4, 26). To mitigate these risks, all ESI will be performed using published guidelines and performed by an experienced provider. (27). These risks are inherent to the ESI, but are not considered study-related.

Procedural Sedation:

Light procedural sedation with the use of midazolam and/or fentanyl is very low-risk but does carry the possibility of cardiac and/or respiratory depression that can lead to hypoxic brain injuries or cardiac arrest. In order to mitigate these risks, all patients and their medical histories will be evaluated by a board-certified anesthesiologist for organ system abnormalities, previous experiences/adverse reactions to medications, drug allergies, current medications, potential drug interactions, time of last oral intake, history of alcohol, tobacco or substance abuse, as is standard of care per American Society of Anesthesiologists guidelines. They will also undergo a focused physical examination including baseline vital signs, auscultation of the heart and lungs and evaluation of the airway. All patients will be continuously monitored by an experienced provider with continuous pulse oximetry, electrocardiogram, capnometry and non-invasive blood pressure during the procedure. Immediately following the procedure, patients will be monitored in a post-procedural area until their vital signs and cognitive function has returned to baseline.(28)

Virtual Reality:

Risks of virtual reality include vertigo, nausea, vomiting and discomfort.(29) If any patient experiences these side effects or wishes to stop, the treatment will be immediately suspended. The participant will then be monitored in the post-procedural area until their symptoms resolve and return to baseline.

2.3.2 KNOWN POTENTIAL BENEFITS

This study is aimed at evaluating the efficacy of virtual reality and assessing the comparative-effectiveness to sedation on painful procedures that could lead to a paradigm shift in how painful procedures are performed. This could in turn lead to a decrease in healthcare expenditures as they relate to procedural costs due to added medications, the need for adequate recovery areas, and the need for extended nursing/physician monitoring during and after the procedure, while improving safety and patient satisfaction. Depending on our findings, we can explore expanding this concept to other settings (e.g. the endoscopy and interventional radiology suites, or even the operating room in patients undergoing minor surgical procedures who are deemed to be at high risk for anesthesia due to medical comorbidities).

This intervention could also be applicable to forward-serving military personnel as treating service members in austere environments carries its own inherent difficulties, as there are often scarce resources available. In some environments, (i.e. care in the battlefield), sedating trauma patients can be challenging or impossible (i.e. no intravenous access) and carries risks such as hypotension and impeding evacuation. The findings in this study may therefore confer unique benefits to military and first-provider populations.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Sedation: As noted above, almost 50% of patients receive sedation routinely for ESI, and with light sedation with low-dose midazolam and/or fentanyl under the monitoring of an anesthesiologist, the risk is minimal. Risk are minimized by having a board-certified anesthesiologist overseeing sedation, and full-scale monitoring of the patient including continuous pulse oximetry and capnography.

Virtual Reality: Patients can and are using VR for acute pain and can buy it over-the-counter (no FDA regulation) because there are minimal risks.

Control group (no VR or sedation): This is default standard of care at all study sties.

3 OBJECTIVES AND ENDPOINTS

Aim 1: To determine the relative efficacy of virtual reality as a distraction modality compared to a sedation group for procedure-related pain, procedural satisfaction, and 1-month pain and functional outcomes.

Aim 2: To determine the relative efficacy of virtual reality as a distraction modality compared to a control group for procedure-related pain, procedural satisfaction, and 1-month pain and functional outcomes.

Aim 3: To determine whether demographic and clinical characteristics are associated with outcome measures

Aim 4: To explore whether virtual reality and lower procedure-related pain scores affect 1-month outcomes. (personalized medicine).

Aim 5: To explore electroencephalogram biomarkers of pain, distraction, and pain tolerance.

Primary Endpoint: Procedure-related pain in 0-10 verbal rating scale (VRS)

Secondary Endpoints: Subcutaneous pain score with 1 mL lidocaine 1% using 25-gauge needle, procedure-related satisfaction on 1-5 Likert scale (1=very unsatisfied, 2=unsatisfied, 3= neither unsatisfied or satisfied, 4=satisfied, 5=very satisfied), procedure-related anxiety based on a1-5 Likert scale (1= extreme anxiety, 2=high anxiety, 3=average or expected anxiety, 2=minimal or mild anxiety, 5=no anxiety), amount of superficial local anesthetic used, EEG-derived spectral edge frequency, time-to-discharge from recovery area (in minutes), patient ability to communicate with provider on a 1-5 Likert scale (1= complete inability to communicate, 2= markedly decreased ability to communicate, 3= slightly decreased ability to communicate, 4= no change in ability to communicate, 5= improved ability to communicate), mean reduction in 0-10 numerical rating scale (NRS) pain scores for average and worst leg pain at 1-month, mean reduction in NRS pain scores for average and worst back pain at 1-month, mean reduction in Oswestry disability index (41) score (0-100%) at 1-month, patient global impression of change (PGIC) (42) at 1-month, adverse events and complications.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. To determine the efficacy of virtual reality as a distraction modality compared to no intervention. 2. To determine the comparative-effectiveness of virtual reality as a distraction modality compared to sedation.	1. Primary: procedure-related pain (0-10 verbal rating scale). 2. Secondary: Adverse events after procedure and at 1-month follow-up, patient ability to communicate with provider during procedure, patient satisfaction with the procedure, procedure-related anxiety, procedure-related pain scores (full procedure and skin wheal), time to discharge from postanesthesia care unit, ,1-month	Procedure-related pain after procedure is recorded when the patient is still on the procedure table (impractical to use a written NRS), and verbal rating scale is validated. We will measure volume of local anesthetic used as this could affect the primary outcome measure. One month is the most common primary endpoint for ESI studies per ACTTION guidelines.(30) The other outcomes are all validated to measure clinically meaningful outcome measures (e.g.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	average and worst NRS pain scores, PGIC (42) and ODI (41) at 1-month, 1-month ODI (41). A 1-month successful outcome will be categorically defined as a 2-point or greater decrease in average leg pain score coupled with a score of $\geq$ 5/7 on the PGIC (42) without the need for co-interventions.	ODI (41) for function associated with back pain, PGIC (42) for patient satisfaction).
Secondary		
Identifying demographic and clinical characteristics that are associated with outcome (i.e. less pain, superior 1-month outcomes)	We will evaluate the effects of the following variables on the primary and secondary outcome measures: anxiety and depression (Hospital Anxiety and Depression Scale, HADS) (31,32), somatic symptoms (Somatic-Symptom Scale, SSS-8),(31, 32) psychiatric co-morbidities, baseline pain and ODI (41) scores, type of procedure, opioid use, military service status (active duty or civilian), type of ESI, and clinical (duration of pain, spinal stenosis vs. herniated disc), social (disability or Worker's compensation, smoking) and demographic factors (age, sex).	All of these have been shown to affect pain and functional outcomes in clinical studies and their effect will be determined in multivariable analysis.
To identify an objective electroencephalogram-derived biomarker of pain	We will assess changes in frontal EEG-derived power spectrum analysis (spectral edge frequency and power in the delta,	EEG directly measures scalp voltage fluctuations due to extracellular ionic currents and has been

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	theta, alpha, and beta bands) recorded in real-time and continuously updated every 1.2 seconds throughout the procedure and compare reported measures of pain with EEG indicators.	used to detect increases in brain activity related to noxious stimulation with a temporal resolution in the order of milliseconds.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This will be a randomized, 3-arm parallel study with a 1-month follow-up. It will enroll patients with lumbosacral radiculopathy who are candidates for and have already agreed to receive a lumbosacral ESI. Patients will be allocated via block randomization (groups of 15-30 depending on site) to one of 3 groups: Group 1 will receive VR (menu of 6 different programs) during their ESI; group 2 will receive light sedation with midazolam 1-5 mg and/ or fentanyl up to 150 mcg at the discretion of the anesthesiologist; and group 3 will receive no intervention. Patients will be sub allocated based on whether they are receiving transforaminal or interlaminar ESI. In all groups, patients will receive superficial local anesthetic with 1% lidocaine using a 25-gauge needle.

Baseline data we will collect include age, duration of pain, pathology (herniated disc vs. foraminal vs. central stenosis), level and type of injection, co-existing psychopathology, medications including opioids, SSS-8 (32), HADS (31), ODI (41), average and worst leg pain over the past week, average and worst back pain, number of concomitant chronic pain conditions, smoking, and secondary gain (disability, Worker's compensation, involvement in a military medical board).

Group 1: The 42 patients allocated to VR will be instructed how to use the simple device and select a program.

Group 2: The 42 patients allocated to receive sedation will be consented on the use of sedation and receive 1-5 mg midazolam and/or fentanyl titrated to effect by a board-certified or eligible anesthesiologist.

Group 3: The 42 patients allocated to the control group will receive superficial local anesthetic only.

The ESI will be done by or under the direct supervision of a board-certified pain medicine physician according to standard protocol as outlined in section 6, using fluoroscopic guidance. Injections will be performed at the level of symptoms as pathology based on MRI findings (physician judgment). Those with unilateral pain will receive transforaminal ESI, while those with bilateral pain will receive interlaminar ESI.

The primary outcome measure will be 0-10 VRS pain score recorded immediately after the procedure. Other data recorded on day 1 will include 0-10 VRS for a 1 mL skin wheal with the 25-gauge needle, amount of local anesthetic (lidocaine 1%) used, procedure satisfaction score on a 1-5 Likert scale (1= very unsatisfied, 2= unsatisfied, 3= neither unsatisfied or satisfied, 4= satisfied, 5= very satisfied), changes in frontal EEG spectral edge frequency recorded in real-time and continuously updated every 1.2 seconds throughout the procedure, ability to communicate with provider on a 1-5 Likert scale (1= complete inability to communicate, 2= markedly decreased ability to communicate, 3= slightly decreased ability to communicate, 4= no change in ability to communicate, 5= improved ability to communicate), procedure-related anxiety on a 1-5 Likert scale (1= extreme anxiety, 2=high anxiety, 3=average or expected anxiety, 2=minimal or mild anxiety, 5=no anxiety)), time-to-discharge from the recovery area, and adverse effects (nausea, vomiting, procedure-related complications, and any unexpected effects related to the sedation (e.g. disinhibition requiring medication or reassurance).

The follow-up visit will occur 1-month post-treatment (24-40-day window period) at which time the patient will be assessed and the other secondary outcome measures obtained. These will include ODI (41), average and worst leg pain score on a 0-10 NRS scale for the past week, average and worst back pain score on a 0-10 NRS scale for the past week, medication usage (medication reduction will be considered cessation of a non-opioid analgesic or > 20% reduction in opioid use),(33) PGIC (7-point Likert scale ranging from 1= no change, to 5= moderately better, a slight but noticeable change, to 7=a great deal better, a considerable improvement that has made all the difference) (42). A binary positive outcome will be a 2-point or greater decrease in average leg pain coupled with a PGIC score $\geq$ 5/7.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We are comparing 2 different modalities to a control (no intervention, default standard of care) to determine their effect on procedure-related pain and satisfaction. To determine efficacy, we are including a control group. To determine comparative-effectiveness, we are comparing VR to sedation, which can increase the risks and costs of an ESI.

4.3 JUSTIFICATION FOR INTERVENTION

VR will be delivered the way it is used recreationally and medically. We are using low-dose midazolam and/ or fentanyl because this is what is most commonly used in clinical practice. Having a control group that receives no intervention will allow us to determine efficacy, and what is typically done at all study sites.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, the single intervention and the 1-month follow-up assessment (or fails to receive the follow-up assessment within the window period).

The end of study is defined as completion of the 1-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3.**

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and lifestyle considerations (see **Section 5.3, Lifestyle Considerations**) and availability for the duration of the study
3. Males and females; ages 18-90 years
4. Lumbosacral radicular pain with a baseline average of leg pain score of $\geq$ 4/10, MRI findings (if available, as they are not mandated before ESI in individuals without red flags) consistent with symptoms, duration of pain > 6 weeks, and no previous lumbar spine surgery.
5. Documented diagnosis of radicular pain caused by herniated disc, central stenosis, foraminal stenosis, degenerative disk disease
6. Willingness to adhere to undergo ESI with either sedation (Midazolam and/or fentanyl) or with virtual reality
7. Able to appear for a follow up visit between 24-40 days following the performed intervention

5.2 EXCLUSION CRITERIA

1. MRI findings discordant with symptoms (absence of herniated disc, spinal stenosis or severe disc degeneration without nerve root impingement (e.g. annular tears) that could explain symptoms)
2. Previous lumbosacral spine surgery at the area affected
3. Prior ESI within the past 6 months
4. Allergy to contrast dye
5. Poorly controlled psychiatric conditions that could affect outcomes (e.g. active substance abuse) or impose a barrier to participation (e.g. anxiety disorder requiring procedural sedation)
6. Morbid obesity (BMI >50)
7. Anticoagulation therapy that cannot be stopped and could warrant a different treatment approach (e.g. caudal injection with a small-gauge needle)
8. Local infection over the needle insertion site or systemic infection

5.3 LIFESTYLE CONSIDERATIONS

Prior to ESI's being performed, participants must be able to:

- Refrain from eating or drinking after midnight on the evening prior to the scheduled intervention

- Have access to a safe ride from after discharge from the post-recovery unit

5.4 SCREEN FAILURE

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include weight loss (BMI <40), progression of their pain to an average of $\geq$ 4/10, new MRI findings consistent with symptoms and resolution of a medical condition that requires anticoagulation. Rescreened participants will be assigned the same participant number as for the initial screening

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- The anticipated accrual rate will be a total of 126 participants across all sites.
- There are 3 participating sites in the U.S. All participants will be enrolled in the U.S.
- Participants will be recruited at outpatient pain clinics at the time they are scheduled for ESI. This will allow patients to take home the consent if they'd like, read it, and discuss it. They will be approached by their treating physician and if interested, an investigator will discuss the trial with them.
- The sites at which participants will be recruited are Johns Hopkins Hospital.
- The principal investigator and the co-investigator in their respective outpatient pain clinics will identify potential participants. Participants will be approached for consent during the participant's regularly scheduled clinic visit.
- Recruitment will occur using the principal investigator's and co-investigator's patients. The study will also be registered on clinicaltrials.gov. There will be no additional advertisements for the study.
- Populations that are considered vulnerable (e.g. prisoners, trainees) will not be recruited for this study.

Lumbosacral radiculopathy is a common disorder that can arise for a variety of reasons in different populations. For this study, the representative population will include potential participants between the ages of 18 to 90 of any race or gender. Because we will only recruit patients who have been evaluated by history, physical exam and imaging, and determined to be a candidate for an ESI, we will only recruit patients from the participating pain centers. To remind practitioners with potential participants about the study, we may consider using brochures and flyers. To promote engage and retention, we will send an appointment reminder and use follow-up phone calls. Study personnel will be trained in presenting the individual's involvement in the study as critical to helping researchers determine the importance of the study in terms of making ESI safe and easier for patients to tolerate.

Participant incentives

- We will not compensate individuals for this study since the ESI is standard of care.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Procedures:

After study eligibility is assessed and informed consent obtained, participants will be randomized based on the above criteria into 3 groups of 42 participants each. A computerized random number generator will be used to randomize study participants. The three groups will receive virtual reality, sedation (midazolam and/ or fentanyl) and no intervention (control) prior to undergoing an ESI. We will also ask patients if they will wear a pEEG self-adhesive sensor placed on their forehead and connected to the bedside monitors. EEG recordings will begin at rest as soon as the monitor is connected prior to superficial anesthesia and will terminate when the sticker is removed when the patient is helped off of the procedure table.

Superficial Anesthesia:

Superficial anesthesia will be performed according to previously published protocols. (34) After the patient is positioned appropriately, they will be prepped and draped in sterile fashion. A skin wheal with 1 mL lidocaine 1% using a 25-gauge needle will be given, and the patient's verbal pain score on a 0-10 scalel will be recorded. Using fluoroscopic guidance, the needle entry site will be identified and marked. Prior to insertion of the needle, the subjects will be informed they will be receiving "a little numbing medication". A total of 3 mL of 1% lidocaine will be administered initially using a 25-gauge, 1.5 inch needle, with additional aliquots of 1-2 mL being administered at deeper levels per the discretion of the physician should a patient exhibit signs of moderate to severe pain (e.g. verbal sounds indicating acute pain, increase in heart rate $\geq$ 5 beats per minute, facial expressions consistent with acute pain). (35-37)

Transforaminal ESI:

Transforaminal ESI will be performed according to previous published protocols. (38, 39) 22-gauge spinal needles will be placed at the inferior aspect of the junction of the transverse process and pedicle using an oblique trajectory. Correct needle position will be confirmed by injecting radiopaque contrast under real-time fluoroscopy. Once the supervising physician is satisfied with the contrast spread, a 3 mL solution containing 40 mg of methylprednisolone, 1 mL of 0.25% bupivacaine, and 1 mL of saline will be slowly injected.

Interlaminar ESI:

Interlaminar ESI will be performed according to previous published protocols. (38, 39) 20-gauge Touhy needles will be used to enter the epidural space using loss of resistance to air or saline. Correct needle position will be confirmed under fluoroscopy with radiopaque contrast dye in multiple projections. Once the supervising physician is satisfied with the contrast spread, a 4 mL solution containing 40 mg of methylprednisolone, 1 mL of 0.25% bupivacaine and 2 mL of saline will be slowly injected.

Sedation:

Sedation will be accomplished by the use of midazolam and/ or fentanyl. We will use a wide range of dosing (1-5 mg for midazolam, up to 150 mcg for fentanyl) to maximize generalizability and account for widespread variability in clinical circumstances, medical practice and patient response (personalized medicine). All medications will be titrated to conscious sedation by a board-certified anesthesiologist. Conscious sedation will allow patients to respond purposefully to verbal commands when aroused by sound of voice and to light tactile stimulation (i.e. light to moderate sedation).

Virtual Reality:

Subjects in the virtual reality group will be offered a variety of immersive environments to choose from (mountains, beach, rainforest and temperate forest). It is estimated from experience and feedback that individuals can learn VR in just a few minutes, and we will ensure that they are able to do this beforehand. Immediately after positioning on the procedure table, subjects in the VR group will be fitted with an HTC headset and headphones with disposable ear covers. Volume will be adjusted so that patients can hear medical team instructions. Medical personal present in the procedure room will be instructed to initiate no further conversation with the patient during the procedure unless responding to patient-initiated conversation. The immersive experience will begin after positioning and will be stopped after the procedure is finished.

For this study the equipment that is already in use in the pain clinic for regular clinical care will be used. This equipment was chosen because it readily available. The study does not aim to study a specific virtual reality device. Subjects will be able to choose their preferred virtual reality program from the device selection.

About 15 minutes prior to the start of the subject's scheduled epidural steroids injection, if the subject is randomized to the virtual reality group the, a study team member will explain the environments available and provide a short demonstration of each environment. The subject will then choose one of the virtual reality environments and the principal investigator, co-investigators, or other study team members will demonstrate to the subject how to use the equipment in the environment that is chosen. Once the demonstration is complete, the subject will be given the opportunity to ask any questions they have about the use of the equipment. Once the patient is positioned on the fluoroscopy table, the patient virtual reality equipment will be given back to the patient and activated until the epidural steroid injection procedure is complete. The equipment will be removed prior to exiting the procedure room.

6.1.2 ADMINISTRATION AND/OR DOSING

All study interventions and procedures will be performed once on all subjects. The dosing and descriptions will be performed as noted above in section 6.1.1.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

All ESI will be performed by either an attending physician, or a trainee under the supervision of a board-certified pain management specialist. The segmental level at which the patient was injected will be determined based on symptoms or radiologic findings. All of the injections will be performed using fluoroscopic guidance and superficial anesthesia in addition to the study intervention (VR or midazolam-fentanyl sedation).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All subjects will be randomized in blocks of between 15 and 30 persons based on the number of anticipated participants at each site. Randomization will be into the three study groups using a computerized random number generator. Sub-randomization will be based on type of ESI (transforaminal vs. interlaminar). This study intervention cannot be blinded to the patient or provider.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Study adherence (compliance) will be determined by the participants completing the follow-up visits required in the protocol.

6.5 CONCOMITANT THERAPY

For this protocol, participants may use their prescribed opioid and non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and other prescribed medications. Medication usage will be assessed and documented at the initial screening, prior to intervention and at the post-procedural follow up visit. No additional procedural or pharmacological interventions will be permitted between the procedure and 1-month follow-up.

6.5.1 RESCUE THERAPY

If a 'rescue' medication is needed for post-procedure pain, NSAIDs or acetaminophen can be prescribed. In individuals on opioids or tramadol, temporary increases may be permitted according to clinical circumstances at the discretion of the physician. These medications will be prescribed as part standard clinical care.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Patients will be discontinued from the study if they do not follow up within the allowed time points. They will also be discontinued if they experience any serious complications from the ESI, virtual reality or sedation. These complications include the following:

ESI:

- Catastrophic injuries (e.g. stroke, spinal cord injury) (incidence < 1 in 1 million)

Sedation:

- Serious complication from the sedation (e.g. cardiac arrest)
- Serious allergic reaction to midazolam or fentanyl

Virtual Reality:

- Vertigo, nausea, vomiting or discomfort requiring discontinuation of intervention

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance or intolerance
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the case report form. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study will be replaced.

If a participant withdraws from the study, we may retain and analyze all coded/de-identified data collected up to the time of withdrawal if the data is necessary to maintain the integrity of the study. However, no further data will be collected after the date of withdrawal.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a follow up visit (day 24-40) and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit (within 24-40 days after the intervention) as well as counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Patients will be screened from 0-28 days prior to enrollment to determine their eligibility. A research nurse or physician investigator will screen all patients (in accordance with HIPAA regulations), who may be identified by providers, physician or self-referrals (e.g. from clinicaltrials.gov), and pre-screening of pain clinic patients. No separate screening protocol will be used. Screening will consist of ensuring that pain scores are within eligibility range, they have been on stable doses of analgesic medications, and that there are no exclusion criteria.

Specific screening and follow-up procedures will include:

- ***Physical examination:*** We will ensure that patients have signs and symptoms consistent with lumbosacral radiculopathy.
- ***Radiological or other imaging assessments:*** Patients must have imaging findings consistent with lumbosacral radiculopathy if they have imaging available (FDA guidelines for lumbar ESI don't mandate imaging in patients without red flags or serious neurological deficits).
- ***Administration of questionnaires or other instruments:*** Questionnaires administered at baseline include HADS (31), SSS-8 (32) and ODI (41). At follow-up visits, ODI (41) will be administered.
- ***Procedures that will be completed during the study as part of regular standard of clinical care****:* Screening history and physical exam, pain score assessment, ODI (41), epidural steroid injection, virtual reality, processed electroencephalography (pEEG) monitoring, and sedation.

Procedures Not Considered Standard of Care

- Randomization into three groups.
- VR and sedation- although we sometimes employ these as part of clinical care during ESI and other procedures, they are not routinely used.
- pEEG- although pEEG is routinely used by anesthesiologists to monitor depth of sedation during painful procedures (43), it not typically used during procedures without sedation. Changes in specific spectral frequencies in the pEEG will be monitored as a surrogate for level of distraction/tolerance from pain and recorded as a secondary outcome measure across

all arms of the study (44, 45).
- The HADS (31) and SSS-8 (32) surveys.

The primary endpoints will occur 4-weeks post-treatment (window period 24-40 days). Patients may be provided with NSAIDs or acetaminophen to treat procedure-related pain. Those already receiving tramadol or opioids may have them temporarily increased for procedure-related pain, at the discretion of the physicians. These medications will be noted, but unless opioids are increased long-term, they should not impact the follow-up period or definition of a positive outcome (a significant increase in opioids (> 15 oral morphine equivalents/ d) will be considered the same as any other concomitant therapy and therefore patients who require this will be considered treatment failures).

8.2 SAFETY ASSESSMENT

Adverse events from the 2 interventions (VR and sedation) will be monitored as they are an outcome measure. Patients receiving sedation will be monitored with continuous pulse oximetry, electrocardiography, blood pressure and capnography, and when vital sign values that are abnormal (> 20% deviation) will be promptly addressed.

ESI are not a study procedure (patients would be receiving an ESI regardless of study participation), but complications will be monitored per routine care during the procedure, with a routine follow-up phone call the day after the procedure, and at the 1-month follow-up. Patients are given instructions as to how to contact the clinic staff if they experience any symptoms they believe may be related to the ESI or intervention and they will be promptly investigated (< 24 h).

A medical monitor has been designated for this study. The medical monitor has the authority to do the following:

i. Stop the research study in progress;
ii. Remove individual(s) from the study; and
iii. Take any steps to protect the safety and well-being of participants until the IRB can assess the problem or event.

CAPT John Hodgson, MD
Medical Monitor
Walter Reed National Military Medical Center
8901 Wisconsin Avenue
Bethesda, MD 20889
301-295-4455
john.a.hodgson.mil@mail.mil

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward or unfavorable medical occurrence in a human subject, including abnormal physical exam signs or symptoms (for example, new-onset numbness in the leg after ESI, or evidence of an infection after an injection) or laboratory findings associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

(Modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice)

Risks from the Virtual Reality
Serious adverse events are extremely rare and have not been reported in a controlled setting. Common risks include nausea, vomiting, vertigo and discomfort (< 2%). These are self-limiting and dissipate after removal of the device.

Sedation
Sedation will be accomplished with low doses of midazolam (1-5 mg) and/ or fentanyl (up to 150 mcg), as patients should be awake or easily arousable, and responsive for this procedure. Light sedation with anesthesiologists present is extremely safe. The most common side effects of midazolam are nausea or vomiting (5%), disinhibition (< 5%), hypotension (< 5%) and prolonged sedation. The most common side effects of fentanyl are nausea and vomiting (< 10%), prolonged sedation, cognitive impairment (< 10%), and respiratory depression (typically in high doses). Midazolam has been shown in clinical studies to actually possess antiemetic properties.(40) Allergic reactions are rare (< 0.5%) and generally easily treated. The likelihood of 'overdosing' with midazolam only in a monitored setting with an anesthesiologist is extremely unlikely (< 1 in 1 million). Flumazenil, a benzodiazepine antagonist, and naloxone, a mu opioid antagonist, are present in the emergency crash carts. In more than 100,000 cases, we have never had a serious cardiovascular (e.g. myocardial infarction) or neurological (cerebrovascular accident) from sedation at Walter Reed or Johns Hopkins, which is similar to other large institutions.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE must meet 1 or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

1. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may

jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

(Modified from the definition of a serious adverse event as per 21CFR312.32(a).)

Planned hospitalization scheduled before the enrollment of study participant is not an SAE.

SAE from sedation: respiratory depression requiring airway support, hemodynamic instability requiring pharmacological intervention.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to

concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in chronic pain management and interventional pain procedures will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. The surveillance of AEs will be through open-ended questions, or participant contact of research personnel or healthcare providers.

All AEs including local and possibly systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The research assistant or nurse at each site will record all reportable events with start dates occurring any time after informed consent is obtained until 48 hours (definitive washout period) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The PI will record all AEs with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. All AEs will be submitted on an AE form to the DCC within 10 working days of the study site investigator becoming aware of the event. Any AE meeting the specified SAE criteria will be submitted on an SAE form to DCC within 72 hours of the study site investigator becoming aware of the event. The investigator should contact the DCC if no confirmation is received. This process applies to both initial and follow-up SAE reports.

Expected events (e.g. dizziness or nausea with sedation, discomfort while wearing the VR headset) will not be reported per the standard process for reporting.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g. hospitalization related to treated) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

AEs that occur at higher rates than expected, or unanticipated SAEs that may affect participants' future care will be communicated to participants via established contact routes.

8.3.8 EVENTS OF SPECIAL INTEREST

All adverse events and severe adverse events will be considered events of special interest and will be reported to the overall study PI and the IRBs. All interventions in this study are frequently used as part of clinical care.

8.3.9 REPORTING OF PREGNANCY

If a participant becomes pregnant before their ESI, they will be withdrawn from the study. This will be reported to the overall study PI within seven business days. If a participant becomes pregnant after their ESI, we will still obtain their 1-month follow-up.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Should any new risk be identified, the study protocol will be modified or even stopped accordingly.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the overall study principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor within seven business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

Events that will be reported within 7 days include:

- "Unanticipated problems involving risks to subjects or others" ("UPIRSO")" that are unexpected, related or possibly related and that place subjects at a greater risk of harm than what was previously anticipated;
- Serious or continuing non-compliance;
- Breaches of confidentiality;
- Incarceration;
- Unresolved subject complaints.

The Johns Hopkins IRB prompt reporting policy is available at: https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/prompt_reporting_policy.html.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint

We hypothesize that virtual reality will be associated with less procedure-related pain and greater satisfaction than the control group. We also hypothesize that the VR group will have comparable procedure-related pain to the sedation group (non-inferiority).

Secondary Endpoints

1. We hypothesize that the VR group will have a shorter time to discharge, and less complications (e.g. nausea) than the sedation group.

2. We do not anticipate overall differences in 1-month outcomes, though we would like to do an exploratory analysis to determine whether people with higher procedure-related pain scores will experience poorer outcomes, as has been shown previously for ESI.(9)

3. We hypothesize that there will be demographic and clinical variables that may determine which individuals will benefit most from VR and sedation (determined via multivariable analysis).

4. We hypothesize that EEG power spectrum analysis will serve as a biomarker for pain with power increasing in higher frequency bands during stimulation, i.e., increased spectral edge frequency, and that this increases will be blunted in the VR group.

9.2 SAMPLE SIZE DETERMINATION

This study was powered to have a 90% chance to detect a 2-point difference in procedure-related pain between the 2 treatment groups (VR and sedation) and the control group (no intervention) assuming the following:

- Mean procedure-related pain score of 5.5 (SD 2.5) in the control group
- Mean procedure-related pain score of 3.5 (SD 2.5) in the treatment groups
- Alpha of 0.05.
- Three equally-sized groups

With these assumptions, 38 patients would need to be enrolled in each group. To account for a 10% dropout rate, we will enroll 42 patients in each group.

We also performed a power analysis to estimate whether our sample size was sufficient to establish non-inferiority between the VR and sedation groups. Assuming the same parameters as above and a minimum detectable effect of a 1.5-point difference in procedure-related pain between the two active treatments, 38 patients per treatment group would be 83% powered to establish non-inferiority at an alpha of 0.05.

9.3 POPULATIONS FOR ANALYSES

The primary analysis with be intention-to-treat, and a per protocol sensitivity analysis will be performed.

9.4 STATISTICAL ANALYSES

The primary outcome will be the procedure-related pain recorded on a 0-10 rating scale immediately after the procedure. We will evaluate normality with the Shapiro-Wilk test. For all three groups, variables will be represented as mean and standard deviation, median (interquartile range), or frequencies and proportions depending on the variable type and distribution. Continuous variables, including the primary outcome, will be compared with analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. For analysis of the primary outcome, post hoc pairwise comparisons will be performed using Tukey's method. The pairwise comparison of the VR versus sedation groups will be used to determine non-inferiority of VR compared to sedation. Dichotomous variables will be assessed by using a chi-square tests or Fischer's exact test for cell count less than 5. All analyses will be performed using an intention-to-treat approach. For the primary and secondary outcome measures, a per-protocol sensitivity analysis will be performed. In all cases, the reasons for failure to follow the protocol will be qualitatively ascertained from individual healthcare providers. Analyses will be performed with STATA version 16 (StataCorp, College Station, Texas, USA). P values of less than 0.05 will be considered statistically significant.

9.4.1 SAFETY ANALYSES

Adverse events will be documented after discharge from the recovery area, in a routine phone call the day after the procedure, and during patients' 1-month follow-up.

Specific AE's that will be monitored include:

- **VR:** Vertigo, nausea, vomiting
- **Sedation:** Vertigo, nausea, vomiting, hemodynamic changes requiring airway support or pharmacological intervention
- **ESI:** Neurological complications (new neurological symptoms), procedure-related pain requiring a medical visit, allergic reaction, vasovagal or syncopal episode

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent will be obtained prior to enrolling patients in the study and continue throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject will be required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

We anticipate that informed consent will take between 25 minutes to obtain per patient, however patients will be given as much time as they need. The consent form is written on an 8th grade reading level, and the study processes will be verbally explained to patients in simple terms to make sure potential participants understand.

The consent process will be documented in the clinical or research record. After the study is completed, participants will be notified of the results.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

An investigator will discuss the study with the patient, they will be given at least 20 minutes to read the consent, and all questions will be answered. Because our study involves the administration of several complicated questionnaires that have NOT been validated in other languages, and translating those documents into another language could undermine validity (translating English language-validated surveys into other languages require validation in a clinical study because slight nuances in the language can result in significant differences in answer). If patients are capable of providing consent for the ESI, they will be considered capable of providing consent for the study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

There will be no early termination since the ESI are being done for standard of care, and our patients often receive sedation to decrease anxiety and procedure-related pain.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples collected during the course of this study. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the study sponsor. Representatives of the participating IRBs may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

No patient identifiers will be attached to any transferrable data or data on spreadsheets that will be analyzed, with a code linking the data contained on the data collection sheets to participants at each site. Each site will designate the person(s) (e.g. a research nurse not involved in data collection or study coordinator) with access to the key. Data between sites will be transferred without any identifiable information (de-identified and coded beforehand, 48 hours after acquisition).

Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR), formerly known as the Collaboratory for Musculoskeletal Injury Rehabilitation Research (CMIRR), which is based out of the Department of Physical Medicine & Rehabilitation at the Uniformed Services University (USU) is serving as the data coordinating center for this research study. As such, authorized staff from MIRROR/USU will have access to the coded research data. Authorized staff from MIRROR/USU will not have access to the electronic Master Lists, the paper research records, or any other form of participant PHI/PII.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the site of collection. The source documents, master code and coded data file will be destroyed 3 years after the study's conclusion. The consent form and HIPAA authorization will be maintained at each local site for a period of six years after the study is completed and then will be destroyed.

Long Term Data Storage & Access:

The de-identified electronic dataset will be maintained by MIRROR/USU and the study team indefinitely or as long it is practicable to maintain. De-identified electronic research data will be securely transmitted from local study teams to the MIRROR/USU via REDCap. REDCap utilizes Secure Sockets Layer (SSL) in addition to other safeguards on its web server to maintain secure communication with end-users.

Once received, the electronic de-identified research data will be stored within an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD)-compliant server.

Access to the de-identified research data will be governed strictly on an individual-by-individual basis within the secure electronic data capture and management system. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Steven P. Cohen	Nelson Hager
Johns Hopkins	Walter Reed NMMC
550 N. Broadway, Suite 301, Baltimore, MD 21205	8901 Wisconsin Ave, Dept. of PM & R, America Building 1st Floor, Bethesda, MD 20889
Phone Number- 410-955-1822	Phone Number- 301-295-7753
Email- scohen40@jhmi.edu	Email- Nelson.Hager@usuhs.edu

10.1.6 SAFETY OVERSIGHT

This is a minimal risk study, and there is no need for additional safety oversight besides the medical monitor.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the site PIs and the medical monitor mid-way through anticipated enrollment completion (i.e. after 63 patients). This will include on-site annual monitoring to ensure protocol fidelity, data verification (e.g. 15% of data samples), adherence to regulatory requirements, and compliance with IRB regulations.

- Details of clinical site monitoring will be documented describing who performed the audit, and the findings.

- IRB-approved study materials, local context forms, changes in the protocol, and enrollment/ outcome information will be communicated at quarterly meetings (already scheduled to discuss studies involving GENEVA Foundation) or via secure e-mail channels (Dr. Cohen, has a secure account through his work at Walter Reed and USUHS, as do investigators at Walter Reed.

Independent audits will not be routinely conducted, but rather occur on an “as needed” basis per the determination of site PI’s, the overall PI, or research nurses. The overall study PI will ensure monitoring practices are performed consistently across all participating sites.

The principal investigator at each site will have sole responsibility of monitoring the data collected during the study for that site. The site principal investigator will be responsible for reporting all adverse events and serious adverse events to the overall study principal investigator.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The following data will be recorded at baseline: age, duration of back pain, inciting event, type of ESI, pathology (herniated disc, central stenosis or foraminal stenosis), concomitant pain conditions, psychiatric co-morbidities, analgesic medications including opioids, smoking status, presence of obesity, military status (civilian, officer, enlisted or retired), average and worst leg pain scores over the past week, average and worst low back pain scores over the past week, HADS (31), SSS-8 (32), and ODI (41).

The primary outcome measure will be procedure-related pain scored on a 0-10 verbal rating scale. A 0-10 verbal rating scale pain score for a standardized 1 ml subcutaneous skin wheal performed with a 25-gauge needle and lidocaine 1% will be recorded at the time of the skin wheal. Secondary outcome measures recorded during the procedure will be electroencephalogram (EEG) changes in specific frequency ranges as an objective biomarker of painful stimulation and the effectiveness of distraction from the painful procedure (44, 45). Processed electroencephalogram (pEEG) and continuous colored density spectral array are routinely used to monitor adequacy of sedation during painful procedures and is readily available for use in the pain clinic (43). A four-channel Masimo SEDLine (Masimo Corporation, Irvine, CA, USA) frontal EEG sensor will be placed with electrode positions corresponding to Fp1, Fp2, F7, and F8 in the

international 10-20 system. The median power across channels is computed and analyzed across the slow/delta (0.1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 12 Hz), beta (12 to 20 Hz), and gamma (>20 Hz) frequency bands. Power spectral analysis using the fast Fourier transform allows quantitative analysis of changes in frequency components that occur over time with stimulation. Spectral edge frequency is calculated as the frequency below which 95% of the power in the spectrum resides and is highly sensitive in identifying a transition between high-voltage slow-activity and low-voltage fast-activity. The pEEG stickers will be placed on the forehead of every patient in all arms of the study. Recording will begin at rest--once patient is prone on the procedural table-- and will continue throughout the procedure until the patient is no longer on the procedural table. Secondary outcome measures recorded in the postanesthesia care unit will include time-to-discharge from recovery unit in minutes, adverse events (e.g. nausea, vomiting, hypotension, vertigo), patient rating on ability to communicate with physician on a 1-5 Likert scale (1=complete inability to communicate, 2=markedly decreased ability to communicate, 3=slightly decreased ability to communicate, 4=no change in ability to communicate, 5= improved ability to communicate), procedure-related anxiety on a 1-5 Likert scale (1=extreme anxiety, 2=high anxiety, 3=average or expected anxiety, 2=minimal or mild anxiety, 5=no anxiety), and procedure satisfaction scale (1=very unsatisfied, 2=unsatisfied, 3= neither unsatisfied or satisfied, 4=satisfied, 5=very satisfied). Secondary outcomes recorded at 1-month will include 1-month average and worst leg pain scores (recorded over the past week), 1-month average and worst LBP pain scores, categorical response (positive or negative, defined above as $\geq$ 2-point reduction in average leg pain score coupled with a PGIC score $\geq$5/7) (42), medication reduction (categorical, defined as > 20% reduction in opioid use or cessation of a non-opioid analgesic) and AE's recorded after the procedure and at 1-month follow-up.

All data will be recorded by a research nurse, research assistant or physician investigator.

The coded electronic research data for this study will be stored in REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT). No PHI/PII will be entered into REDCap.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The

noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All deviations will be addressed in study source documents and reported to overall study PI. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Study findings will be entered into the registry after completion, and de-identified datasets may be available from the overall PI upon request.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Conflicts of interest will be disclosed in the appropriate section of each site's IRB application. The overall study principal investigator assessed sites and potential study group members for potential conflicts of interest. It has been determined that no study group members have a potential conflict of interest.

10.2 ADDITIONAL CONSIDERATIONS

Additional Info - MIRROR/USU:

This research study is being conducted as part of Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR), formerly known as the Collaboratory for Musculoskeletal Injury Rehabilitation Research (CMIRR), which is based out of the Department of Physical Medicine & Rehabilitation (PM&R) at the Uniformed Services University (USU). MIRROR is focused on advancing musculoskeletal injury (MSI) rehabilitative care within the military healthcare system in order to reduce the burden MSIs have on military readiness and to ultimately enhance the operational capabilities of the armed forces. MSIs affect approximately 800,000 service members annually and result in 25 million days of limited duty. These conditions are the primary reasons for medical discharge/downgrade and result in 34% of medical evacuations from theatre. MIRROR was developed as a means to study risk factors of common MSIs, generate prevention strategies, optimize treatments, and establish return-to-duty criteria that is based on scientific evidence rather than case-specific clinical judgment alone.

MIRROR involves interdisciplinary and inter-service partnerships, the Department of Defense (DoD), and several major academic medical centers. To ensure military mission focus and scientific relevance, MIRROR is guided by a steering committee composed of members from the Joint Program Committees (JPCs) at the U.S. Army Medical Research and Materiel Command (USAMRMC), military operational leaders, and experts in musculoskeletal medicine from the military and civilian communities. MIRROR aims to be the world's leader in military relevant musculoskeletal injury care research.

Currently, research projects are being deployed at more than 19 military and civilian treatment facilities nationwide.

MIRROR/USU is serving as the Data Coordinating Center for this study and will also be providing remote regulatory support. Staff from MIRROR/USU will not interact with human subjects and will not have access to the paper research records or any identifiable research data. Deidentified research data will shared with MIRROR/USU and maintained indefinitely for possible use in future research.

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ACOVA	Analysis of Variance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMIRR	Collaboratory for Musculoskeletal Injury Rehabilitation Research
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ESI	Epidural Steroid Injection
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LBP	Low back pain
MIRROR	Musculoskeletal Injury Rehabilitation Research for Operational Readiness

NMCSD	Naval Medical Center San Diego
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
WRNMMC	Walter Reed National Military Medical Center

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

1. Manchikanti L, Pampati V, Hirsch JA. Retrospective cohort study of usage patterns of epidural injections for spinal pain in the US fee-for-service Medicare population from 2000 to 2014. BMJ Open. 2016;6(12):e013042.

2. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Comparative Analysis of Utilization of Epidural Procedures in Managing Chronic Pain in the Medicare Population: Pre and Post Affordable Care Act. Spine (Phila Pa 1976). 2019;44(3):220-32.

3. Physician Payment Rates Compared to 2017 Rates American Society of Interventional Pain Physicians2017 [Available from: *https://www.asipp.org/Fee%20Schedules/2018PhysiciansFinal.pdf*.

4. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. Anesthesiology. 2011;114(4):918-26.

5. Schneider BJ, McCormick Z, O'Brien D, Bunch M, Smith CC, on behalf of the Spine Intervention Society's Patient Safety C. Patient Safety: Conscious Sedation. Pain Medicine. 2018;19(9):1872.

6. Statement on Anesthetic Care During Interventional Pain Procedures for Adults.: American Society of Anesthesiologists; 2016 [Available from: *https://www.asahq.org/-/media/sites/asahq/files/public/resources/standards-guidelines/statement-on-anesthetic-care-during-interventional-pain-procedures-for-adults.pdf*.

7. Childers CP, Maggard-Gibbons M. Understanding Costs of Care in the Operating Room. JAMA Surg. 2018;153(4):e176233.

8. Lang EV, Rosen MP. Cost analysis of adjunct hypnosis with sedation during outpatient interventional radiologic procedures. Radiology. 2002;222(2):375-82.

9. Cohen SP, Hameed H, Kurihara C, Pasquina PF, Patel AM, Babade M, et al. The effect of sedation on the accuracy and treatment outcomes for diagnostic injections: a randomized, controlled, crossover study. Pain Med. 2014;15(4):588-602.

10. Hoffman HG, Richards TL, Van Oostrom T, Coda BA, Jensen MP, Blough DK, et al. The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. Anesth Analg. 2007;105(6):1776-83, table of contents.

11. Nguyen TN, Nilsson S, Hellström AL, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. J Pediatr Oncol Nurs. 2010;27(3):146-55.

12. Soo MS, Jarosz JA, Wren AA, Soo AE, Mowery YM, Johnson KS, et al. Imaging-Guided Core-Needle Breast Biopsy: Impact of Meditation and Music Interventions on Patient Anxiety, Pain, and Fatigue. J Am Coll Radiol. 2016;13(5):526-34.

13. Graff V, Cai L, Badiola I, Elkassabany NM. Music versus midazolam during preoperative nerve block placements: a prospective randomized controlled study. Reg Anesth Pain Med. 2019.

14. Smith HS, Colson J, Sehgal N. An update of evaluation of intravenous sedation on diagnostic spinal injection procedures. Pain Physician. 2013;16(2 Suppl):SE217-28.

15. Kim N, Delport E, Cucuzzella T, Marley J, Pruitt C. Is sedation indicated before spinal injections? Spine (Phila Pa 1976). 2007;32(25):E748-52.

16. Ahmed SU, Tonidandel W, Trella J, Martin NM, Chang Y. Peri-procedural protocols for interventional pain management techniques: a survey of US pain centers. Pain Physician. 2005;8(2):181-5.

17. Neal JM, Bernards CM, Hadzic A, Hebl JR, Hogan QH, Horlocker TT, et al. ASRA Practice Advisory on Neurologic Complications in Regional Anesthesia and Pain Medicine. Reg Anesth Pain Med. 2008;33(5):404-15.

18. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med. 2008;70(8):890-7.

19. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain. 2003;106(1-2):127-33.

20. Bernards CM, Hadzic A, Suresh S, Neal JM. Regional Anesthesia in Anesthetized or Heavily Sedated Patients. Regional Anesthesia & Pain Medicine. 2008;33(5):449.

21. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, et al. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. Anesthesiology. 2015;122(5):974-84.

22. Cohen SP, Bhaskar A, Bhatia A, Buvanendran A, Deer T, Garg S, et al. Consensus practice guidelines on interventions for lumbar facet joint pain from a multispecialty, international working group. Reg Anesth Pain Med. 2020.

23. Ikonomidou E, Rehnström A, Naesh O. Effect of music on vital signs and postoperative pain. AORN J. 2004;80(2):269-74, 77-8.

24. Hoffman HG, Seibel EJ, Richards TL, Furness TA, Patterson DR, Sharar SR. Virtual reality helmet display quality influences the magnitude of virtual reality analgesia. J Pain. 2006;7(11):843-50.

25. Patterson DR, Hoffman HG, Palacios AG, Jensen MJ. Analgesic effects of posthypnotic suggestions and virtual reality distraction on thermal pain. J Abnorm Psychol. 2006;115(4):834-41.

26. Boswell MV, Shah RV, Everett CR, Sehgal N, McKenzie Brown AM, Abdi S, et al. Interventional techniques in the management of chronic spinal pain: evidence-based practice guidelines. Pain Physician. 2005;8(1):1-47.

27. Management ASoATFoCP, Medicine ASoRAaP. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010;112(4):810-33.

28. Gross JB, Bailey PL, Connis RT, Coté CJ, Davis FG, Epstein BS, et al. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology. 2002;96(4):1004-17.

29. Nichols S, Patel H. Health and safety implications of virtual reality: a review of empirical evidence. Appl Ergon. 2002;33(3):251-71.

30. Cohen SP, Wallace M, Rauck RL, Stacey BR. Unique aspects of clinical trials of invasive therapies for chronic pain. Pain Rep. 2019;4(3):e687.

31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.

32. Gierk B, Kohlmann S, Kroenke K, Spangenberg L, Zenger M, Brähler E, et al. The somatic symptom scale-8 (SSS-8): a brief measure of somatic symptom burden. JAMA Intern Med. 2014;174(3):399-407.

33. Cohen SP, Hayek S, Semenov Y, Pasquina PF, White RL, Veizi E, et al. Epidural Steroid Injections, Conservative Treatment, or Combination Treatment for Cervical Radicular Pain: A Multicenter, Randomized, Comparative-effectiveness Study. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2014;121(5):1045.

34. Cohen SP, Mao J, Vu TN, Strassels SA, Gupta A, Erdek MA, et al. Does pain score in response to a standardized subcutaneous local anesthetic injection predict epidural steroid injection outcomes in patients with lumbosacral radiculopathy? A prospective correlational study. Pain Med. 2013;14(3):327-35.

35. Möltner A, Hölzl R, Strian F. Heart rate changes as an autonomic component of the pain response. Pain. 1990;43(1):81-9.

36. Stojanovic MP, Cheng J, Larkin TM, Cohen SP. Psychophysical measurements during lumbar discography: a heart rate response study. J Spinal Disord Tech. 2007;20(5):387-91.

37. de Knegt NC, Pieper MJ, Lobbezoo F, Schuengel C, Evenhuis HM, Passchier J, et al. Behavioral pain indicators in people with intellectual disabilities: a systematic review. J Pain. 2013;14(9):885-96.

38. Cohen SP, White RL, Kurihara C, Larkin TM, Chang A, Griffith SR, et al. Epidural steroids, etanercept, or saline in subacute sciatica: a multicenter, randomized trial. Ann Intern Med. 2012;156(8):551-9.

39. Cohen SP, Hanling S, Bicket MC, White RL, Veizi E, Kurihara C, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study. BMJ. 2015;350:h1748.

40. Rodolà F. Midazolam as an anti-emetic. Eur Rev Med Pharmacol Sci. 2006;10(3):121-6.

41. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66: 271-3.

42. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004; 27: 26-35.

43. Sun Y, Wei C, Cui V, Xiu M, Wu A. Electroencephalography: Clinical Applications During the Perioperative Period. Front Med 2020; 7.

44 Cowen R, Stasiowska MA, Laycock H, Bantel C. Assessing pain objectively: the use of physiological markers. Anaesthesia 2015; 70(7): 828-847.

45. Ploner M, May ES. Electroencephalography and magnetoencephalography in pain research—current state and future perspectives. Pain 2018; 159(2): 206-2011.