1. Title
   Virtual Reality for Pain Management Study

2. Principal Investigator
   Mark Powers
   Powersmb
   Department of Psychology

3. Purpose

Drug overdose is the leading cause of accidental death in the United States (US) and prescription pain reliever addiction is driving this epidemic (Center for Disease Control and Prevention [CDC], 2015). There are enough opioid prescriptions written each year to provide every single adult American one bottle of pills (e.g., 259 million prescriptions in 2012) (CDC, 2014) and 78 Americans die every day from an opioid overdose (CDC, 2016). Pain is the most universal medical complaint with 25% of US adults reporting a day-long episode of pain over the previous month and 10% reporting the pain lasted a year or more (National Center for Health Statistics, 2006). Pain and its sequela (including those directly linked to opioid use/abuse) cost the US economy 61.2 billion per year (Stewart, Ricci, Chee, Morganstein, & Lipton, 2003). Accordingly, finding new methods of reducing pain is a priority for the US government. Indeed, on March 18, 2016 the CDC released new guidelines for reducing opioid prescriptions (Dowell, Haegerich, & Chou, 2016) and on March 29, 2016 the White House released a document detailing the actions needed to address this public health problem (The White House, 2016). Both of these documents call for non-medication methods of pain management.

Virtual Reality (VR) is one effective non-pharmacological method that reduces acute and chronic pain. A systematic review of 11 randomized controlled trials (i.e., gold standard for evaluating intervention efficacy) showed that VR reduced pain more than credible control interventions (Malloy & Milling, 2010). Importantly, pointing to room for improvement to current VR interventions for pain, this analysis showed that the level of pain reduction was dependent on how realistic the virtual environments were. There are two primary problems with current VR technology that prevent large-scale use and effectiveness. First, current VR technology uses animated (cartoon like) environments (see Figure 1). Patients report this quality prevents full immersion. Studies have shown that many users complain that the computer generated virtual reality (VR) stimuli looks unrealistic, eccentric and too much like a video game (Kwon, Powell, & Chalmers, 2013). Virtual reality environments have been traditionally created by programmers using video game assets and computer generated imagery (CGI). While CGI can be used to make intricate virtual environments, unless there is a team of

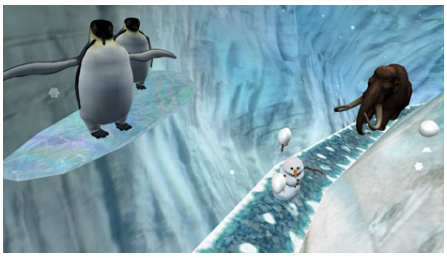

Figure 1. Example of current VR

Figure 2. Example of current VR

expert digital artists, the virtual stimulus may end up looking rudimentary and exhibit a number of graphical glitches, which could prove distracting in therapy. Furthermore CGI often suffers from the uncanny valley effect: the tendency of CGI representations of people to be viewed as unsettling as the representations become more lifelike. Second, current CGI VR technology is bulky and costly requiring a large computer setup with multiple screens (approximately $30,000 for a setup; see Figure 2). Recent advances in VR technology can address both of these concerns, and thus there is potential to develop a more cost-effective application.

Figure 3. 360-degree

Figure 4. New affordable delivery

Our team has been working with virtual reality for 10 years now conducting several large randomized controlled trials (Powers & Emmelkamp, 2008; Meyerbröker, Powers, van Stegeren, & Emmelkamp, 2012; Powers et al., 2013; Tart et al., 2013). Two major recent innovations are central to this proposal. First, the realism possible in VR has dramatically increased with the use of 360-degree 3D HD film environments. 360-Degree Video VR is a radical filmmaking technology that can turn live action footage into a 360-degree environment that users can interact with. 360-Degree Video VR is made by filming with an array of multiple HD cameras carefully arranged to capture all angles in a 360-degree area of a live action event (see Figure 3). Then those angles are stitched together in post-production into a 360-degree texture sphere and the sphere is then mapped to the head tracker on the users HDM. Leading to the effect that when a user turns his head, their view of the live action video footage turns with them in real time (e.g. if the user looks down, the camera pans down and the user sees the floor) allowing the user to look around anywhere in the 360 degrees of filmed footage of the live action event. The benefit of 360-Degree Video VR as opposed to CGI VR is that it is photo realistic, does not suffer from the uncanny valley effect of CGI, and is able to capture nuances of real life fears that are hard to reproduce with CGI. In addition, the projected cost of the end product is approximately $500. This enhanced level of immersion has the potential to dramatically improve the efficacy to reduce acute and chronic pain (see above). Second, deployment of the resulting content to patients is now much smaller and inexpensive (e.g., $99 for a Samsung Galaxy Gear VR (see Figure 4) or $20 for Google Cardboard systems). This technology makes VR accessible to anyone with a smartphone.

The current study seeks to test the efficacy of the standard animated/CGI VR versus the enhanced 360-degree 3D HD film versions of VR in reducing pain in hospital patients. To this aim we will enroll 201 adult participants experiencing pain University Medical Center Brackenridge (UMCB), Dell Seton Medical Center (DSMC), Baylor Scott & White Medical Center Temple (BSWMCT), and randomly assign them to the enhanced (360-Degree Video VR) film condition (n = 67), the standard (animated/CGI film) condition (n = 67), or the waitlist

condition (n = 67). We anticipate we will need to recruit and consent a total of 500 participants due to the anticipated number of screen failures (due to inclusion/exclusion criteria). We hypothesize that the film VR will show greater pain reductions and increased functioning relative to both the animated VR and the waitlist condition.

4. Procedures

Hospital Study Visit
Data collection will be completed in a single visit to the participant at University Medical Center Brackenridge Hospital, Dell Seton Medical Center, or Baylor Scott & White Medical Center Temple and an online follow-up questionnaire e-mailed to the participant approximately one-week after study visit completion. If email is not available for the follow-up survey, participants will be reached by telephone. Total participation in the hospital visit will be approximately 1 hour. The follow-up survey will take participants 10-15 minutes to complete. Prior to gathering data, research personnel will receive proper training in order to interact with the hospital patients and will follow all hospital procedures during the study visit.

Recruitment
Our Seton PI, Dr. Thomas Caven, will connect research personnel with hospital staff at UMCB and (DSMC) who care for patients experiencing pain. Hospital staff will refer patients to research personnel that meet eligibility criteria for the study and may be a potentially eligible participant. Patient information necessary to conduct an in-person recruitment visit by study personnel (patient name and hospital room number) will be shared by hospital staff with research personnel through the standard secure email (Ascension Secure E-mail Portal) or texting (TigerText) applications used by UMCB and (DSMC). Both of these applications are regularly used by UMCB and (DSMC) staff to share Protected Health Information (PHI) with hospital staff. Ascension Secure E-mail Portal and TigerText keep messages confidential and are HIPAA compliant. Additionally, potential participant information may be shared with research personnel during in-person morning hospital rounds. Hospital staff may supply potential participants with information regarding the study found in the Recruitment Announcement, but will not be involved with direct recruitment. All direct recruitment will be conducted by research personnel. This method of recruitment is the standard used by UMCB and (DSMC) and is the preferred manner of recruitment by hospital staff.

Our BSWMCT PI, Dr. Crystal Lantrip, will connect research personnel with hospital staff at BSWMCT who care for patients experiencing pain. Hospital staff will refer patients to research personnel that meet eligibility criteria for the study and may be a potentially eligible participant. Patient information necessary to conduct an in-person recruitment visit by study personnel (patient name and hospital room number) will be shared by hospital staff with research personnel in-person, over the phone, or in email over the secure hospital network. All direct recruitment will be conducted by research personnel.

Research personnel will meet with the potential participant in their hospital room to recruit the patient for the study. If the patient is interested in participating, the research personnel will conduct the in-person study visit at that time, or return at a time specified by the patient. At the start of the study visit research personnel will go over the consent form with eligible participants and answer any questions they may have about the study procedures. Participants will be able to continue on with the study if they are able and willing to give signed informed consent. Following consent, participants will asked, if they are willing, to complete and sign the HIPAA Research Authorization form to permit research personnel to access their medical records. Information collected from the medical records will include self-report pain ratings, medication information (names, doses, and timing), hospital room number, phone number, email address, date of birth, medical diagnosis information, and medical progress notes. If participants refuse to sign the HIPAA Research Authorization, they will still be allowed to participate in the study, but their medical records will not be accessed by research personnel.

During a 15-minute baseline, participants will be assessed for consciousness by study personnel (Glasgow Coma Scale & abbreviated Mini Mental Status Exam) and then complete a short battery of questionnaires to obtain demographic, treatment, and prior media use information, and to assess their mood, average pain, and pain interference levels. All assessments will be delivered on an electronic iPad or on paper. All assessments are designed to be able to be delivered orally if participants cannot use the iPad or utilize a pen or pencil.

Conditions

Participants will be randomized to the 360° 3D HD video VR film condition, animated video VR condition, or waitlist condition. Those randomized to the waitlist group will complete all study procedures except the VR exposure. After completion of the study visit, we will give those in the waitlist condition the option of experiencing the 9-minute VR video of their choosing.

360° 3D HD Video Virtual Reality

360° Video Virtual Reality (360° -VVR) refers to a three-dimensional, immersive film environment that people can interact with. Typically users interface with virtual reality via a digital head mounted display (HMD) (see Figure 5.) that immerses the user in the virtual world by blocking their vision of the outside world, so that the user can only see the three dimensional images projected on the digital display in front of their eyes.

Figure 5. Head mounted display

A key component of virtual reality is that users can guide their sensory input of the multimedia environment in a way similar to how they guide their senses in real life. The HMD typically incorporates a head tracker that is mapped to a virtual "camera" view of the three-dimensional multimedia environment so that when users turn their heads, their view of the multimedia environment shifts with them (e.g. if users look down, the camera pans down and the users see the floor). As such, unlike a 2D film, 360° - VVR is an interactive 360° viewing experience. While you can turn your head away from the experience of watching a television, with a virtual reality head mounted

display, if you turn your head you will only see more of the virtual world. 360°-VVR can provide powerful interactive experiences for users but until recently, the hardware necessary for virtual reality could cost tens of thousands of dollars. However in the last five years virtual reality headsets have become almost as cheap as cellphones and Google cardboard makes it even cheaper by allowing people to use their android phones as do-it-yourself VR headsets. Thus, VR headsets are no longer limited to well-funded labs but in the grasp of individuals. This technology could mean that reducing pain in hospital patients through use of VR is a practical and economical reality.

The VR treatment in this study will be administered using a Samsung Gear VR headset. The Gear VR is a new, affordable virtual reality headset, that when coupled with a Samsung Galaxy smartphone can deliver photorealistic VR footage easily to participants in a hospital setting.

Treatment

Following the acquisition of consent and the baseline assessments, participants will be outfitted with a Samsung Gear VR headset. Before the headset is placed on the patient's head, the patient will be given the option to wear a plastic shower cap over their head for the headset straps to rest on. This was recommended by the Infections Control Preventionist at DSMC. The shower cap is not required if the patient does not desire to wear one. The research assistant will help them adjust the headset. If the participants record any discomfort, the research assistant will attempt to adjust the settings on the Samsung Gear VR. If the participant finds that regardless of the settings, they cannot watch the video comfortably, they will be thanked for their time and their participation in the study will end.

After the headset is properly calibrated, the participant will receive instructions that they are about to view VR footage of central Texas locations. At the same time, they will be told that during the task they should try to imagine that they are actually at the location experiencing the scenery first hand. Additionally, participants will be instructed not to exert their body in any capacity that may cause additional pain while experiencing the virtual environment. They will be instructed that if at any time they become uncomfortable or wish to stop using the Gear VR, they may do so at anytime. Before watching the video, patients will be outfitted with a pair of headphones. The headphone ear cushions will be covered with sanitary disposable headphone covers. The covers on each ear cushion will be disposed of in a hospital trash can after each patient is finished watching the VR video.

Participants in the enhanced film condition will view 9 minutes of VR film footage of representative Austin scenes. The 9 minutes of footage will be alternating 30 second clips of Hamilton Pool Preserve in Dripping Springs, TX, a rower on Lady Bird Lake in Austin, TX, Red Bud Isle in Austin, TX, and Zilker Botanical Gardens in Austin, TX. These locations were picked for their beauty and likeliness for participants to be immersed in and distracted by the aesthetically pleasing footage.

Participants in the standard animated video VR film condition will view the same content for the same duration as in the enhanced film condition, but the footage will be animated instead of photorealistic. Participants in the waitlist condition will be instructed to wait for 9 minutes.

Post-Treatment Assessments

Following the 9 minutes of VR exposure or waiting, participants in each condition will complete post-treatment assessments for 5-10 minutes. These assessments will measure pain, presence, mood, negative effects of VR, absorption, human presence, participant's prior familiarity with the locations depicted in the VR video, and their attitude toward the VR session immediately after the treatment. Nausea, dizziness, eyestrain, and head pain is being assessed in an effort to identify the incidence of this component of simulator sickness sometimes associated with VR use (Kennedy et al., 1992). Following the Post-Treatment assessments, the Follow-Up Pain Questionnaire & Present Mood Questionnaire will be administered 10 minutes following the treatment. These follow-up assessments are in place in order to track the lasting pain reduction from the VR treatments.

Open Interview

Following the Follow-Up Pain Questionnaire & Present Mood Questionnaire, participants will be asked to provide any feedback they had from the VR treatment and to describe their experiences throughout the experiment. Was the treatment comfortable? Do they think it could help them manage pain? The interview will be left in an open format to allow participants more freedom in expressing themselves.

Cleaning of VR Headset

After each study visit with a patient, research personnel will wipe down the face cushion and the plastic exterior of the VR headset using a PDI Sani Cloth Plus Germicidal Wipe. This is the sanitization procedure recommended by the Infection Control Preventionist at DSMC.

Collecting Data from Medical Records

After completion of the study visit, research personnel will collect data from the patient's medical records if the patient completes and signs the HIPAA Research Authorization form. All PHI obtained from medical records (self-report pain ratings, medication information (names, doses, and timing), hospital room number, phone number, email address, date of birth, diagnosis information, and medical progress notes) will be accessed electronically by research personnel on a Seton computer at the hospital. Electronic data from medical records will be entered directly into a password protected tracking sheet on UT Box and maintained by research personnel.

One-week E-mail Follow-up

One-week after participating in the experiment participants will be e-mailed a series of follow-up questionnaires that will include the Follow-Up Pain Questionnaire, Present Mood Questionnaire, and Participant Satisfaction Survey. If participants cannot be reached by email, research personnel will contact them via telephone or a follow-up in person interview.

Hospital Study Visit Overview

1. Obtain Informed Consent
2. Baseline Assessment (15 minutes)
    a. Asses consciousness
        i. Glasgow Coma Scale
        ii. Mini Mental Status Exam
    b. Demographic Questionnaire
    c. Media Use Survey
    d. Personal Health Questionnaire-8
    e. Pre-Treatment Pain Questionnaire
    f. Present Mood Questionnaire
3. Treatment Conditions
    a. Film VR condition (30 minutes)
        i. Samsung Gear VR information session
            1. Participants will receive information describing the Gear VR and instructed to fully engage with the VR video.
        ii. Samsung Gear VR Fitting
            1. Gear VR will be adjusted to participant's head
        iii. Watch 9 minute 360° 3D HD VVR film
        iv. Administer Post-Treatment Assessments (5-10 minutes)
            1. Post-Treatment Pain Questionnaire
            2. Present Mood Questionnaire
            3. Presence Inventory
            4. Absorption Survey
            5. Attitudes Toward the Experience Survey
            6. Human Presence Survey
            7. Location Familiarity Survey
        v. Wait 10 minutes
        vi. Administer both the Follow-Up Pain Questionnaire & Present Mood Questionnaire (3-5 minutes)

b. Animated VR condition (30 minutes)
    i. Samsung Gear VR information session
        1. Participants will receive information describing the Gear VR and instructed to fully engage with the VR video.
    ii. Samsung Gear VR Fitting
        1. Gear VR will be adjusted to participant's head
    iii. Watch 9-minute animated film
    iv. Administer Post-Treatment Assessments (5-10 minutes)
        1. Post-Treatment Pain Questionnaire
        2. Present Mood Questionnaire
        3. Presence Inventory
        4. Absorption Survey
        5. Attitudes Toward the Experience Survey
        6. Human Presence Survey
        7. Location Familiarity Survey
    v. Wait 10 minutes
    vi. Administer both the Follow-Up Pain Questionnaire and Present Mood Questionnaire (3-5 minutes)
c. Waitlist condition
    i. Participants will be directed to wait patiently for 9 minutes
    ii. Administer both the Follow-Up Pain Questionnaire & Present Mood Questionnaire (3-5 minutes)
    iii. Participants can choose to watch one of the two treatment VR videos for 9 minutes.
        1. Administer Post-Treatment Pain Questionnaire

4. Open Interview (3-5 minutes)
5. One-week e-mail follow-up (10-15 minutes)
    a. Follow-Up Pain Questionnaire
    b. Present Mood Questionnaire
    c. Participant Satisfaction Survey

a. Location

All data collection will take place at University Medical Center Brackenridge, Dell Seton Medical Center, or Baylor Scott & White Medical Center Temple. Upon completion of data collection, data analysis will take place at UT Austin in the College of Liberal Arts (CLA) building.

i) New location name: Baylor Scott & White Medical Center Temple
ii) BSWMCT has an active FWA. Assurance number is: FWA00003358.
iii) Dr. Crystal Lantrip will be the PI at BSWMCT. Dr. Lantrip is a Clinical Neuropsychologist. Dr. Lantrip will have access to identifiers and will also aide in recruitment as described in the recruitment section (Page 16, Section 6, Part "e"). Dr. Lantrip will be trained on all study procedures in order to be able to run patients through the study should the Research Coordinator onsite be unavailable.
    (1) E-mail: Crystal.Lantrip@BSWHealth.org
    (2) Phone Number: 254-724-6414
iv) IRB of Record Name: Baylor Scott and White IRB –Gold.
    (1) IRB Contact Information
        (a) Tracy Troxell, IRB Program Manager
        (b) Email: Tracy.Troxell@BSWHealth.org
        (c) Phone: 254-771-4869
v) Baylor Scott and White IRB – Gold requires the Principal Investigator to report unanticipated problems involving risks to subjects or others and other study related information to them and any other IRB with oversight.
vi) Baylor Scott and White IRB – Gold will retain oversight of the study activity at their institution.

b. Resources

The project is funded internally through the Longhorn Innovation Fund for Technology (LIFT Grant).

Dr. Thomas Caven will be our Seton PI and resource for running the study at University Medical Center Brackenridge and Dell Seton Medical Center. Dr. Caven is the Vice President of Medical Affairs and Medical Director, Dell Seton Medical Center at the University of Texas and University Medical Center Brackenridge. Through the hospital he is donating the time of the hospital staff and the VR headset (Galaxy phone with Samsung Gear VR). Dr. Caven will have access to identifiers and will also aide in recruitment as described in the recruitment section (page 14, Section 6, part "e"). Dr. Caven will not directly recruit participants for the study.

c. Study Timeline

Data collection will begin once IRB approval has been granted (tentatively November 2016) and has an anticipated end date of August 2017. Results will be disseminated by September 2017.

5. Measures
   Assessments will be collected as outlined in the table below

Table. Assessment Schedule			
Assessments	**Study Visit Before Treatment**	**Study Visit After Treatment**	**1-Week Follow-Up**
Glasgow Coma Scale	X		
Abbreviated Mini Mental Status Exam	X		
Demographics Questionnaire	X		
Media Use Survey	X		
Personal Health Questionnaire-8	X		
Pre-Treatment Pain Questionnaire	X		
Present Mood Questionnaire	X	X	X
Post-Treatment Pain Questionnaire		X	
Presence Inventory		X	
Absorption Survey		X	
Attitudes Toward the Experience Survey		X	
Human Presence Survey		X	
Location Familiarity Survey		X	
Follow-Up Pain Questionnaire		X	X
Open Interview		X	
Patient Satisfaction Survey			X

- *Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974)*
  The Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) is a commonly used instrument in clinical practice and provides a structured method for assessment of the level of consciousness. The GCS has good reliability and well-established cross-sectional construct validity (Prasad, 1996).

- *Mini Mental Status Exam (MMSE) (Folstein, Folstein, & McMugh, 1975)*
  The Mini Mental Status Exam (Folstein et al., 1975) is a questionnaire used extensively in clinical and research settings to measure cognitive impairment. We will be using an abbreviated version in combination with the GCS to assess for adequate consciousness for participation in the study.

- *Demographics Questionnaire*

Participants will be asked to provide standard demographic information (i.e. age, gender, race/ethnicity, level of education, etc.). Participants will also be asked about hearing and visual impairment as well as their history of motion sickness.

- *Media Use Survey*

  The Media Use Survey is a brief 4-question survey aimed to determine the participant's typical prior use of TV, online videos, and video games. The measure also asks about prior use of a virtual reality headset.

- *Personal Health Questionnaire-8 (PHQ-8)*

  The Patient Health Questionnaire 8-Item (PHQ-8) is a brief self-report measure of major depressive disorder (Koneke, Spitzer, & Williams, 2001). The PHQ-8 is considered to be a valid measure of depression for population-based studies and clinical populations (Kroenke et al., 2009), with a cut off score of equal to or greater than 10 considered diagnostic for current depression. The PHQ-8 is derived from the PHQ-9 by removing the last question regarding suicidality.

- *Pre-Treatment Pain Questionnaire*

  The Pre-Treatment Pain Questionnaire will be used to assess the participant's pain prior to receiving VR treatment. It is derived from the Brief Pain Inventory (BPI; Cleeland and Ryan, 1994; Cleeland et al., 1996) and contains Numerical Rating Scales (NRS) aimed at assessing the participant's pain intensity, pain quality, pain interference, and pain relief, as recommended by the IMMPACT recommendations for outcome measures in clinical pain trials (Dworkin et al., 2005). The NRS is one of the most common measures for assessing pain, and has been a validated outcome measure of pain intensity (Breivik, Björnsson, & Skovlund, 2000; Breivik et al., 2008). The NRS was also chosen because it could be administered orally if patients cannot use their hands to write or use the iPad.

- *Present Mood Questionnaire*

  The Present Mood Questionnaire will be sued to assess the participant's current mood. The survey uses a labeled (0-10) NRS to measure the extent that the participant feels sad, anxious, happy, and tranquil.

- *Post-Treatment Pain Questionnaire*

  The Post-Treatment Questionnaire will be used to assess the participant's pain during and following the virtual reality treatment. The NRS pain assessment questions are identical to the Pre-Treatment Pain Questionnaire, except questions are altered to specify pain the participant experienced during the VR treatment.

- *Presence Inventory*

  The Presence Inventory is adapted from The ITC-Sense of Presence Inventory (Lessiter et al., 2001) and The Igroup Presence Questionnaire (IPQ). It will be used to assess the degree of Spatial Presence (The ITC-Sense of Presence Inventory), Ecological Validity (The ITC-Sense of Presence Inventory & IPQ), and Negative Effects (The ITC-Sense of Presence Inventory).

- *Absorption Survey (adapted from Agarwal, & Karahanna, 2000)*
  The Absorption Survey (adapted from Agarwal, & Karahanna, 2000) is a 12-item NRS that will be used to measure participant engagement with the virtual world. Participants rate the degree to which they agree with the statements on a 1-10 scale, with 0 being "strongly disagree" and 10 being "strongly agree".

- *Attitudes Toward the Experience Survey (adapted from Sundar, 2000)*
  The Attitudes Toward the Experience Survey (adapted from Sudnar, 2000) is a 12-item NRS that will be used to measure the participant's attitude toward the VR experience. Participants rate the degree to which they agree with the statements on a 1-10 scale, with 0 being "strongly disagree" and 10 being "strongly agree".

- *Human Presence Survey (adapted from Basdogan, Ho, Srinivasan, & Slater, 2000)*
  The Human Presence Survey (adapted from Basdogan, Ho, Srinivasan, & Slater, 2000) is a 2-item measure that will be used to assess the extent that participants felt they were with other people during the VR session.

- *Location Familiarity Survey*
  The Location Familiarity Survey is a 1-item measure that will be used to assess the participant's prior familiarity with the locations depicted in the virtual reality videos.

- *Follow-Up Pain Questionnaire*
  The Follow-Up Questionnaire will be used to measure the participant's pain in the 4 follow-up pain assessments following the VR treatment. It will also be administered during the 1-week follow-up survey. It is identical to the Post-Treatment Pain Questionnaire, but asks for pain ratings during the last 10 minutes instead of during the VR session.

- *Open Interview*
  The Open Interview will be comprised of brief open-ended questions designed to collect general patient feedback regarding their thoughts about the virtual reality treatment upon conclusion of the study visit. It will be used to guide future research methods.

- *Patient Satisfaction Survey*
  The participant satisfaction survey will be used to assess participant acceptability and satisfaction of the virtual reality treatment 1-week following completion of the study. It has both questions utilizing a Numeric Rating Scale as well as open-ended questions and will be used to guide future research methods. The survey will also include the Patient Global Impression of Change scale (PGIC; Guy, 1976). This measure is a single-item rating by participants of their improvement with treatment during a clinical trial on a 7-point scale that ranges from "much better" to "much worse" with "no change" as the mid-point. There has been widespread use of the PGIC in recent clinical pain trials (e.g. Dunkl et al., 2000; Farrar et al., 2001) and the data provide a responsive and readily

interpretable measure of participants' assessments of clinical importance of their improvement or worsening over the course of a clinical trial (Dworkin et al., 2005).

6. Participants
   a. Target Population

   Our target enrollment is 201 participants who complete all study procedures. We will recruit 500 participants 18 years of age and older in order to enroll 201 participants to account for dropouts and ineligible participants. Participants will be patients experiencing current pain that is not related to day-to-day, normal experiences (such as minor headaches, sprains, and toothaches) at University Medical Center Brackenridge or Dell Seton Medical Center in Austin, TX, or Baylor Scott & White Medical Center Temple in Temple, TX, that are referred to the study by hospital staff.

   The final number of participants enrolled in each of the three study conditions is expected to be 67 participants.

   b. Inclusion/Exclusion

Inclusion Criteria

- 18 years of age and older
- Reports experiencing current pain not typical of day-to-day experience during Pre-Treatment Pain Questionnaire at the onset of study visit by answering "Yes" to the first question of the questionnaire. There is no specific threshold of how much pain the participant must be in to be eligible for this study. The participant must be experiencing current pain that is not related to day-to-day, normal experiences (such as minor headaches, sprains, and toothaches).
- Scores a 15 on the Glasgow Coma Scale and a 7 or above on the abbreviated Mini Mental Status Exam.
- Patient experiencing pain at University Medical Center Brackenridge or Dell Seton Medical Center in Austin, TX referred to the study by hospital staff.
- Willing and able to provide informed consent and participate in the study visit and study follow-up questionnaire.
- Able to position head completely upright (90 degrees from the ground) in order to view the entirety of the Virtual Reality video.

Exclusion Criteria

- Hearing or visually impaired where they cannot use the Samsung Gear VR.
- Does not report experiencing current pain during Pre-Treatment Pain Questionnaire at the onset of study visit.
- Scores below a 15 on the Glasgow Coma Scale and/or below a 7 on the abbreviated Mini Mental Status Exam
- Limited mental competency and the inability to give informed, voluntary, written consent to participate.

- History of motion sickness or cyber sickness and unwilling to watch a 10-minute virtual reality video because of it.
- Unable to position head completely upright (90 degrees from the ground).
- History of seizures.
- Lesions, rashes, or open wounds on face, head, neck, or ears.

c. Benefits

There is no direct benefit to the participant for participating in this study. The possible benefit for the participant from participating in this study is reducing pain they may be experiencing. Societal benefits include diversifying pain management treatments for patients in hospitals to include VR programs. The use of portable and affordable VR technology could be distributed widely and eventually reach patients in all medical and even in home settings. Society could further benefit from using virtual reality for pain management by reducing the use of prescription opioids and subsequently potentially lessening the number of prescription pain reliever drug overdoses in the United States.

d. Risks

The risks associated with participating in this study are minimal. Potential risks include:

- The assessment instruments may cause mild distress because of their focus on emotional topics associated with mental health and pain. If participants are interested in receiving referals for this distress, they will be instructed to alert research personnel and the personnel will provide the participant with a referral list. Participants can stop the study at any time as a result of this distress with no consequence.
- Cyber sickness, a form of motion sickness, is a potential risk of virtual reality use. Symptoms can include blurred vision, sweating, eyestrain, salivation, headaches, vertigo, dizziness, nausea, and vomiting. Symptoms are temporary and resolve within a few minutes to a few hours. For this reason, we also limit the exposure length to 9-15 minutes. Participants can discontinue the exposure at any time if they experience any of these symptoms. Less than 10% of participants report such symptoms using the old technology. In addition, we expect fewer of these symptoms with this new technology. Participants may stop the study at any time if they begin to experience any of these possible symptoms from experiencing video virtual reality.

Protection of Human Participants from Research Risk

Adequacy of Protection Against Risks: The PI, Mark Powers, Ph.D., is available for intervention as needed and back-up plans are established including referral to a hospital emergency department. These safety procedures have been effective in dealing with adverse physical and mental health events in previous and ongoing studies. Upon study completion, all participants will be referred to follow-up care if needed.

Persons who express suicidal ideation (or other forms of serious threat to themselves or others, or who are gravely disabled due to a mental disorder) at any time they are in contact with the study personnel will receive the usual ethically and legally appropriate courses of action. This would include assessment of the seriousness of danger or disablement, referral for immediate crisis management (e.g., hotlines, crisis centers, hospitals), or contacting emergency psychiatric teams or police if necessary. Study personnel who have direct contact with study participants (e.g., telephone interviewers, laboratory assessors, scheduling staff) will be trained in methods of crisis management.

To deal with the potential risk of loss of privacy (judged to be minimal), we will maintain confidentiality by numerically coding all data, by disguising identifying information, and by keeping all data in locked file drawers. Participant information will be accessible only to research staff. Identifying information will not be reported.

Collection and Reporting of AEs and SAEs

Information regarding AEs will be obtained by questioning or examining the participant. At each visit all new complaints and symptoms (i.e., those not existing prior to signing of informed consent) will be recorded on the AE Form. Pre-existing complaints or symptoms that increased in intensity or frequency after having signed the Informed Consent Form will be entered on the AE Form also. All AEs will be characterized in terms of their start and stop dates, start and stop times, intensity, action taken on Intervention, relationship to Intervention, participant outcome and whether or not the AE led to a Serious Adverse Event (SAE). Any clinically relevant increase or decrease to the intensity or frequency of a reported AE will trigger a separate entry on the AE Form. If the event meets the definition of an SAE, the procedure for reporting SAEs will be followed; the event will not be reported on the AE Form also incase the start and stop dates are equal to the start and stop dates of the SAE.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

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

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious too.

All serious events occurring between signing of the Informed Consent Form by the participant and signing of the End of Trial Form by the investigator, except those pre-specified in the protocol, will be reported as soon as practical (within 24 hours of awareness) to the IRB. This includes serious events, which could be associated with the trial procedures, even if occurring outside the treatment period.

Follow-up of SAEs, which occurred during the trial, will in principle take place until resolution of the SAE. Under this protocol, the following event(s) will not be considered as (an) SAE(s) and will not be entered on the SAE form:

- Pre-planned hospitalizations for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of a clinical trial. These pre-planned hospitalizations will be entered on the medical history form, including the condition requiring hospitalization.
- Hospitalizations for uncomplicated delivery.

All SAEs (i.e. including serious events occurring outside the treatment period) will be reported as soon as practical (within 24 hours of awareness) to the IRB. Reporting of an SAE will be done by means of the SAE form. For each SAE, the investigator fills out this SAE form (as complete as possible) and sends the form and all available supporting documentation by fax or scan.

e. Recruitment

Our Seton PI, Dr. Thomas Caven, will connect research personnel with hospital staff at UMCB and DSMC who care for patients experiencing pain. Hospital staff will refer patients to research personnel that meet eligibility criteria for the study and may be a potentially eligible participant. Patient information necessary to conduct an in-person recruitment visit by study personnel (patient name and hospital room number) will be shared by hospital staff with research personnel through the standard secure email (Ascension Secure E-mail Portal) or texting (TigerText) applications used by UMCB and DSMC. Both of these applications are regularly used by UMCB and DSMC staff to share Protected Health Information (PHI) with hospital staff. Ascension Secure E-mail Portal and TigerText keep messages confidential and are HIPAA compliant. Additionally, potential participant information may be shared with research personnel in-person. Hospital staff may supply potential participants with information regarding the study found in the Recruitment Announcement, but will not be involved with direct recruitment. All direct recruitment will be conducted by research personnel. This method of recruitment is the standard used by UMCB and DSMC and is the preferred manner of recruitment by hospital staff.

Our BSWMCT PI, Dr. Crystal Lantrip, will connect research personnel with hospital staff at BSWMCT who care for patients experiencing pain. Hospital staff will refer patients to research personnel that meet eligibility criteria for the study and may be a potentially eligible participant. Patient information necessary to conduct an in-person recruitment visit by study personnel (patient name and hospital room number) will be shared by hospital staff with research personnel in-person, over the phone, or in email over the secure hospital network. All direct recruitment will be conducted by research personnel

Research personnel will meet with the potential participant in their hospital room to recruit the patient for the study. If the patient is interested in participating, the research

personnel will conduct the in-person study visit at that time, or return at a time specified by the patient.

f. Obtaining Informed Consent

The consent form will be handed to the potential participant (paper procedures) or shown to the participant on an iPad (electronic procedures), and they will be given time to read through the form. Research personnel will go over the consent form and answer any questions about the study. If the participant agrees to participate, they will be asked to type in their name and date, and give informed signed consent using either their finger directly onto the iPad or a stylus pen, or asked to sign the paper consent form.

Participants will either receive a paper copy or be emailed a consent form for their records, depending on their preference.

A waiver of HIPAA Research Authorization will be used in order to collect initial screening data from hospital staff to recruit potential participants for the study. The HIPAA waiver is only being requested for recruitment purposes. A waiver of HIPAA authorization is appropriate for this study as the research could not be practically conducted without having access to the name and hospital room number of potentially eligible participants. This PHI will be supplied to research personnel by the hospital staff, and without it, research personnel would have no way of recruiting potential participants in the study.

Participants will sign a HIPAA Research Authorization to allow research personnel to access participant medical records. Information collected from the medical records will include self-report pain ratings, medication information (names, doses, and timing), hospital room number, phone number, email address, date of birth, medical diagnosis information, and medical progress notes. If participants refuse to sign the HIPAA Research Authorization, they will still be allowed to participate in the study, but their medical records will not be accessed by research personnel.

7. Privacy and Confidentiality

Keeping all data securely stored will protect participants' privacy to the best of our abilities. Data forms and accompanying narrative summaries will undergo a systematic and rigorous editing process before they are keyed into the database. The research assistants routinely evaluate the data and discuss any problems and questions with the study staff and Dr. Powers at regular weekly team meetings. Accuracy of data entry will be ensured by a standard double-entry procedure. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated one time a month during the final team meeting of the month. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available. Additionally, our hard copy record systems, as described previously, will be maintained in fire-resistant locked cabinets.

This study will utilize a web page-internet data collection and management system used in previous work. All data for the current study including demographic information, diagnoses, and participant and clinician rated measures will be directly entered into an electronic case report form (eCRF).

The eCRF will consist of a series of separate web pages for study personnel and participants. A series of passwords will be programmed to ensure that participants are unable to access pages reserved for study personnel. The eCRF will be constructed so that all requested information must be entered into each page in the fields provided, or the system will not permit access to the next page. The system is designed so that only completed eCRFs can be transmitted. If information for a field is either not available or not applicable, the system will require that it be documented as such in the eCRF. Field parameters will be specified such that suspect values are either disallowed or flagged for the immediate attention of the study directors and Principal Investigators.

All study data (eCRF and data entry from paper forms) will be collected and managed using REDCap electronic data capture tools or Qualtrics Survey Software hosted at University of Texas at Austin.

REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap is a HIPAA compliant company, and servers are stored in a tier one data storage facility that includes adequate security measures.

Like REDCap, Qualtrics is a generalized survey/form service permitting the creation of survey instruments, distribution of the surveys, data storage and analysis. Qualtrics meets stringent information security requirements as set out by UT Austin. Qualtrics servers are protected by high-end firewall systems, and scans are performed regularly to ensure that any vulnerabilities are quickly found and patched. Complete penetration tests are performed yearly. All services have quick failover points and redundant hardware, with complete backups performed nightly. Data are stored and processed in a specific secure location. HITECH (Health Information Technology for Economic and Clinical Health Act) updated HIPAA rules to ensure that data are properly protected and best security practices followed. Qualtrics safeguards all customer data, and uses secure data centers to ensure the highest protection as per HITECH requirements.

Confidentiality of the Data or Samples

a. Data collection
    - Self-report measures and consent forms will be collected online via REDCap or Qualtrics on an iPad or by paper.
    - All structured interviews or clinician-administered scales will be administered by a research associate or other trained member.
b. Secure storage

- All participants' information will be coded with a participant number and their information will be stored in locked file drawers. A master list of names and numbers (phone number, email address, date of birth, age, hospital room number) will be kept in a separate location and is used to facilitate the collection of follow-up data. Only senior project staff will have access to the master list linking names and code numbers.
- All self-report measures will be collected online using REDCap or Qualtrics directly into a computer. Hand-entered measures will be entered twice and a program will run to flag discrepancies. Discrepancies will be presented to the PI, whom makes final decisions about coding. We will implement cleaning routines that will be used on scanned data in order to identify miscoded or duplicate variables.
- All paper documents will be kept in locked cabinets stored in locked rooms accessible only our lab personnel.
- All PHI used for recruitment purposes, (patient name and hospital room number), will be maintained by the Research Coordinator and secured in a locked file cabinet, within a locked office.
- All PHI obtained from medical records (self-report pain ratings, medication information (names, doses, and timing), hospital room number, phone number, email address, date of birth, diagnosis information, and medical progress notes) will be accessed electronically by research personnel on a Seton computer at the hospital. Electronic data from medical records will be entered directly into a password protected tracking sheet on UT Box and maintained by research personnel.

c. Length of time data is kept
    - All self-report, interview, and clinician data will be kept and maintained until five years after the publication of study results or seven years after the last patient contact (whichever is longer) in line with the guidelines of the American Psychological Association.
    - Signed, electronic and paper consent forms and the master key file will be kept for 3 years after the last participant completes the study.
    - All PHI used for recruitment purposes, (patient name and hospital room number), will be kept until the patient has been contacted and either completed the study visit, declined to participate, or been deemed ineligible. At this point, the patient name and hospital room number of participants who did not enroll in the study will be shredded.
    - All PHI obtained from medical records will kept until the completion of the study, estimated to be 05/31/2018. At this point, all PHI obtained from medical records will be deleted.

d. Confidentiality of the data
    - For all self-report measure, we can ensure confidentiality by encrypting identifying and personal information of study participants and keeping that

information entirely separate from their coded data. Lastly, the database administrator will export requested data to the investigators in a file format that can be easily read by most statistical packages.

- The data, in aggregate form only, may be used for future research or be made available to other researchers for research purposes not detailed in this study.

e. Destruction of data
   - All self-report, interview, clinician data, HIPAA Research Authorization forms, and electronic consent forms will be deleted from REDCap or Qualtrics.
   - The master key file will be deleted and removed from the computer database.
   - Paper consent forms and HIPAA Research Authorization Forms will be shredded.

8. Compensation
   Participants will not be compensated for their participant in our study.

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