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Efficacy of virtual reality assisted guided imagery (VRAGI) in a home setting for pain management in patients with advanced cancer: protocol for a randomised controlled trial

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ABSTRACT

Introduction Patients with advanced cancer often experience high levels of debilitating pain and pain-related psychological distress. Although there is increasing evidence that non-pharmacological interventions are needed to manage their pain, pharmacologic modalities remain the preferred treatment . Guided imagery is a form of focused relaxation that helps create harmony between the mind and body and has been shown to significantly improve cancer pain. Our study presents Virtual Reality Assisted Guided Imagery (VRAGI) as a complementary treatment modality to manage chronic pain in patients with cancer. We will conduct a randomised controlled trial to test its impact on patients with advanced cancer in a home setting.

Methods and analysis We will recruit 80 patients from Prisma Health, a tertiary-level healthcare centre based in Greenville, South Carolina, USA. The prospective 2×2 randomised controlled trial will randomise participants into four groups: (1) VRAGI, (2) laptop-assisted guided imagery, (3) VR (no guided imagery) and (4) laptop (no guided imagery). Patients allocated to VR groups will be trained to use a head-mounted display that immerses them in 3D audio–video content. The non-VR group will use a laptop displaying 2D video content. We will collect measures before and during the 3-week intervention as well as 3 weeks after the intervention ends. Measures will include patient-reported outcomes of pain, anxiety, depression and fatigue in addition to opioid use. The primary objective of the current study is to assess the efficacy of VRAGI on pain in the home setting. The secondary objective is to assess the efficacy of VRAGI on opioid use, anxiety, depression and fatigue.

Ethics and dissemination This study was approved by the Prisma Health Institutional Review Board (#Pro00114598) in November 2021. All participants enrolled in the study will provide written informed consent. Dissemination will be through peer-reviewed publications and conference presentations.

Trial registration number NCT05348174, clinicaltrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a novel design that combines the use of immersive virtual reality (VR) technology with guided imagery processes to treat chronic pain in patients with advanced cancer.
⇒ We propose a reproducible intervention that can be self-administered in a home setting, thus eliminating the need for trained personnel, transportation modalities or healthcare facilities.
⇒ VR content will be preloaded onto all-in-one (no tethered computer required) head-mounted displays, thus eliminating the need for access to the internet and decreasing the variability of the intervention.
⇒ We will collect patient-reported outcomes on pain, anxiety, depression, fatigue and opioid use, but not continuous user feedback or biofeedback.
⇒ This study focuses on patients <65 years of age with advanced cancer which allows us to focus on a large group of patients; however, this may limit the overall generalisability of the findings.

INTRODUCTION

Patients with advanced cancer often experience debilitating pain and pain-related psychological distress. Advanced cancer can be defined as a diagnosis of cancer that cannot be cured.[1] Severe pain is reported in 59% of patients undergoing cancer treatment, 64% of patients with advanced disease and 33% of patients after curative treatment, thus making it the most common symptom in patients with cancer.[2] Unrelieved pain greatly affects patients' comfort, daily activities, motivation, interactions with family and friends and overall quality of life.[3 4] Undertreatment of pain remains a major issue.[5–7]

The International Association for the Study of Pain notes pain is experiential

and is associated with biological, psychological and social factors.[8] Cancer pain, in particular, is multifactorial and encompasses physical, psychosocial and spiritual dimensions,[9] rendering pharmacotherapy alone often ineffective.[10–12] Despite increasing interest in non-pharmacological interventions such as guided imagery, mindfulness and acupuncture, medications remain the preferred intervention to treat pain.[13] As such, the Center for Disease Control and Prevention and National Comprehensive Cancer Network (NCCN) strongly recommends non-pharmacologic interventions in the management of cancer pain.[14 15] More specifically, the NCCN Adult Cancer Pain guidelines recommend practitioners consider referring patients to a licensed mental health professional trained in cognitive behavioural therapy (CBT), hypnosis, biofeedback, mindfulness-based stress reduction and/or guided imagery in addition to treating the multifactorial nature of pain, as such therapies could serve as adjunct therapies that reduce the need for medications.[16]

Guided imagery is a form of focused relaxation that can help create harmony between the mind and body. It is a way of focusing one's imagination to create calm, peaceful images and provide a 'mental escape'.[17] Guided imagery has been shown to reduce some degree of cancer pain.[18–22] In a randomised controlled non-pharmacological trial that used guided imagery, the intervention group reported a significant decrease in pain, distress, anxiety and depression when compared with usual care.[23] More recently, therapeutic virtual reality (VR) has emerged as a promising and evidence-based treatment modality for assisting with the reduction of cancer pain.[24] Immersive VR involves wearing a head-mounted display (HMD) and virtually transporting users into alternative realities.[25] Zeng *et al* provided concrete evidence of the efficacy of VR-based interventions in acute cancer care settings.[26] Several other studies have also shown that VR is safe and associated with measurable improvements in cancer-related symptoms.[27–31] These symptoms include pain, fatigue, anxiety, depression and cognitive dysfunction.[27–31]

VR studies in cancer pain have been limited to short-term trials, small-sized samples and suboptimal research designs, which reduces the interpretability and generalisability of their findings.[32] The majority of these studies were performed in acute care settings and only reported the immediate effects of VR-based interventions rather than longer-term effects.[33] Also, most VR research focuses on mere distraction. Limited research exists on the use of skills-based VR that employs principles of guided imagery, meditation and CBT.[34] Additionally, there is a lack of at-home VR-based interventions that focus on the patient population with advanced cancer. Researchers have not fully discovered the multiple advantages of home-based delivery, which include the elimination of exposure to communicable diseases,[35] need to train personnel,[36] experience of noisy hospital environments that can be disruptive for coping with pain,[37] and transportation issues.[38]

Our VR programme utilises guided imagery and mindfulness to provide a mind–body approach to alter the experience of pain caused by cancer and its treatment. This programme is expected to impact cancer pain in three ways. First, guided imagery involves a top–down neurological process of direct regulation by the brain of physiological functions, which affects the attention and preconscious processes likely involved in the perception of pain and prevents nociceptive pain inputs from reaching the higher cortical structures responsible for pain perception.[39–42] Second, mindfulness processes may reduce the psychological significance of pain, even if reports of pain intensity are not reduced.[43] Third, guided imagery engages dissociation, which likely activates endogenous opioids to physically reduce pain intensity and psychologically reduce pain sensations.[44]

The primary objective of the current study is to determine the impact of virtual reality assisted guided imagery (VRAGI) dimensions on pain in the home setting. The secondary objective is to assess the efficacy and safety of VRAGI dimensions on opioid use, anxiety, depression, and fatigue. Our hypotheses include:

(H1) VRAGI will provide greater immediate improvements in pain compared with versions presented on a laptop or without guided imagery.

(H2) VRAGI will provide greater sustained improvements in pain weekly and 3 weeks after the intervention compared with versions presented on a laptop or without guided imagery.

METHODS AND ANALYSIS

Design

This prospective, 2×2 randomised controlled trial will be conducted with participants from Prisma Health, a tertiary-level healthcare centre based in South Carolina, USA. We evaluate the effects of two two-level factors: 'Guided imagery' and 'VR immersion' (table 1, figure 1).

The four arms of the study consist of: (1) VRAGI, (2) laptop-assisted guided imagery (AGI), (3) VR (no guided imagery but with the natural imagery and soundscape) and (4) laptop (no guided imagery with the natural imagery and soundscape). We will recruit 80 participants from Prisma Health Cancer Institute, outpatient oncology and palliative care clinics. Randomisation of participants will be performed via Research Electronic Data Capture

Table 1 Study arms

		GI	
		Included	***Absent***
Immersion level	*High (VR)*	VRAGI	VR (no GI)
	Low (Laptop)	Laptop AGI	Laptop (no GI)

AGI, assisted guided imagery; GI, guided imagery; VR, virtual reality; VRAGI, virtual reality assisted guided imagery.

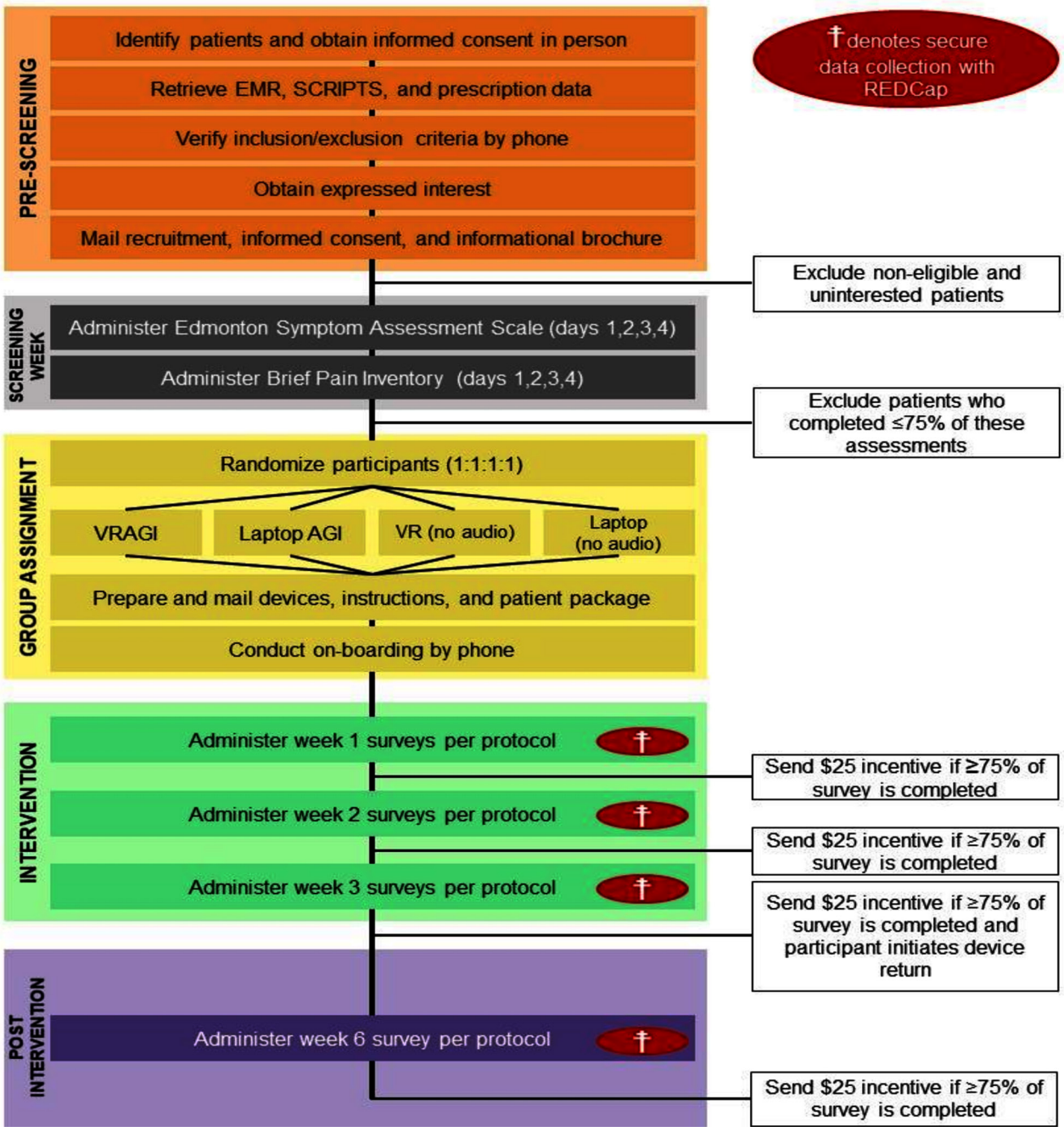

Figure 1 Study design. VR, virtual reality; VRAGI, Virtual Reality Assisted Guided Imagery.

(REDCap) using a 1:1:1:1 allocation between the four study groups. During recruitment, we will randomly assign participants who fulfil the inclusion and exclusion criteria to one of the four study groups while balancing age, gender and cancer progression. Eligible participants in the VRAGI or VR (no GI) arms will be trained to use the HMD at home. Participants in the other two groups will use a laptop to watch the same visual content shown in the HMDs. All participants will be provided with the necessary devices (HMD or laptop) and wired headphones to ensure they can hear the guided imagery and/or natural soundscape. Treatment sessions will last 15–20 min and will occur once a day for 3 weeks.

Our sample size of 80 is based on an observed mean for pain at baseline of 7 (SD=1, range=0–10), significance level of 0.05, power of 0.8 and anticipated main effect size of 0.6 in G*Power.[45 46] Since recruitment is staggered and the study is completed in batches due to the limited availability of VR headsets, any attrition will be overcome in future waves of recruitment. We used the Standard Protocol Items: Recommendations for Interventional Trials checklist when writing our report.[47]

Setting and sample

The study will be conducted remotely. The principal investigator (PI) will conduct monthly meetings with

institutional clinical and research staff to provide education about the study and facilitate recruitment. Potential participants will be referred by the cancer institute staff. Flyers and word-of-mouth from clinical and research staff will be utilised for recruitment. Collection of all patients' reported data is performed electronically via REDCap, a secure web application. The three sequential study phases include screening, intervention, and postintervention.

Screening phase

The study coordinator will screen consented participants for eligibility using patient electronic health records (EHRs) and conduct a phone assessment to verify eligibility. Consent will occur 2–3 weeks prior to the intervention start date (online supplemental material 2). The study coordinator will screen participants using the following criteria:

1. >18 years of age.
2. Advanced cancer, defined as cancer that is incurable including locally advanced and metastatic cancers, with no plan for resection during the study period.
3. Baseline pain score Edmonton Symptom Assessment Scale (ESAS) ≥4 (mean score during the screening week).
4. Able to provide consent and willing to comply with all study procedures, as well as comprehend spoken and written English.
5. Have access to a compatible Android, iOS smartphone, personal laptop or desktop computer (excluding tablets) to complete surveys and respond to emails.

Participants who meet the above criteria will effectively be ruled eligible unless they meet any of the following exclusion criteria:

1. Have a condition that interferes with VR usage including history of seizure, facial injury precluding safe placement of an HMD or other visual or hearing impairment that impacts ability to participate.
2. Used VR for therapeutic applications (ie, relaxation, meditation or distraction from pain) regardless of whether this was self-administered with a personal device or in the context of a clinical study.
3. Underwent a surgical procedure in the past 4 weeks.
4. Have a neurocognitive disorder according to medical history.
5. Have brain metastases.
6. Have a prognosis of <3 months from the time of enrolment per treating oncologist.
7. Experience current substance abuse.
8. Experienced complex childhood trauma.
9. Diagnosed with serious mental illness as defined by the National Institute of Mental Health.
10. >65 years of age to reduce the possibility of cybersickness in VR.[48]

Eligible participants who do not opt out will be emailed a recruitment letter and informational brochure. On receipt of the signed consent form (online supplemental material 2) and prior to randomisation, participants will be enrolled in a 7-day screening week. This screening week is designed to evaluate willingness and ability to respond to emailed survey questionnaires, which participants are required to respond within the week (online supplemental material 1).

The average score of symptoms on ESAS will be used to calculate the baseline (preintervention) symptom intensity. A screening failure for this study is defined as a participant who completed fewer than 75% of the forms provided during the screening week.

Intervention phase

All participants who successfully complete the screening week will receive a second phone call from the study coordinator for an onboarding session. HMDs will be mailed out to participants in the VR arms in advance of this call and asked to watch a 10-min video on how to use the HMD. Participants will have unlimited access to these training videos. The study coordinator will discuss the patient packet, which will contain all study instructions and surveys. The study coordinator will be available to support participants throughout the study via phone call and email support. All participants are allowed to undergo any concomitant treatment prescribed by their provider outside of those listed in the exclusion criteria.

The Meta Quest 2 HMD (formerly named Oculus Quest 2) will be used with the VR groups. Participants will be instructed to sit down while viewing VR content. This is a stand-alone headset that requires no additional hardware (ie, phone or computer) to operate and playback the intervention. Also, the VRAGI sessions are preloaded so that the internet is not needed. Before participants receive their HMD, it will be sanitised via skin-friendly antibacterial cleaning wipes and exposing the HMDs to ultraviolet light treatment in a CleanBox for 1 min, killing 99.99% of all bacteria, including COVID-19 and its variants[49 50] (online supplemental material 1).

The visual landscape consists of a computer-generated immersive virtual world with nature-based imagery (ie, trees, birds, mountains, water) and accompanying soundscapes with guided imagery (figure 2). The guided imagery consists of an omnipresent vocal narration that overlaps with some of the imagery in the virtual scene and steers users through mental escape, redirection of attention, anxiety alleviation, and a non-judgmental acceptance psychological process.

Participants will complete the sessions in the correct calendar order (ie, spring then summer then fall). The content was developed by an interdisciplinary collaboration of physicians, mental health counsellors, human systems engineers and VR content experts. Participants in all four arms of the study will visually see these virtual worlds. In the two groups containing guided imagery, there will be an accompanying nature-based soundscape (ie, water flowing, birds chirping, narration). In the two groups containing no guided imagery, there will be the same nature-based soundscape provided.

Figure 2 Images from virtual reality assisted guided imagery programme based on three seasons.

Postintervention phase

Participants will be asked to fill out ESAS and Brief Pain Inventory (BPI) at 6 weeks.

Study outcomes

The primary and secondary outcomes are provided in table 2. Patient-reported outcomes (PROs) will be measured using standardised symptoms assessment tools: the ESAS and BPI. Metrics for measuring overall acceptability are demonstrated in table 3. PROs will be collected along with two VR-specific questionnaires: a client satisfaction questionnaire and VR side effects questionnaire as shown in table 4.

Demographic data will be collected using EHR, including date of birth, age, sex, marital status, education, household income, employment status, insurance status and place of birth. Additionally, an EHR review will be used to collect participants' medical record number, type of cancer (diagnosis), TNM stage, primary histology (eg, adenocarcinoma), estimated prognosis, goal of treatment (curative/palliative), medication use (eg, anxiety and anti-nausea), radiation regimen, chemotherapy regimen, comorbidities (eg, diabetes and hypertension), medical history of neurocognitive disorders, history of stroke or dementia, neurologic conditions, neuropathy, the Eastern Cooperative Oncology Group Scale and Karnofsky Performance Status.[51] Prescription data will be extracted from the Prescription Monitoring SCRIPTS database. Participants will also be required to maintain a daily opioid diary to assess opioid use.

The BPI has nine items related to pain and asks participants to answer a variety of questions, such as illustrating on a human diagram where they feel pain and answering questions about their level of pain (1=no pain to 10=pain as bad as you can imagine) and asking to what degree pain interferes with things like mood or sleep with the

Table 2 Study outcomes

Measure	Outcome type	Source
Brief Pain Inventory (BPI)[53] Pain	Primary	REDCap
Edmonton Symptom Assessment Scale (ESAS)[54] Pain	Primary	REDCap
Edmonton Symptom Assessment Scale (ESAS)[54] Anxiety	Secondary	REDCap
Edmonton Symptom Assessment Scale (ESAS)[54] Depression	Secondary	REDCap
Client Satisfaction Questionnaire (CSQ)	Secondary	REDCap
VR Questionnaire (VRQ)	Secondary	REDCap
Milligram morphine equivalent (MME)	Secondary	EMR/SCRIPTS

EMR, electronic medical record; REDCap, Research Electronic Data Capture.; SCRIPTS, South Carolina Reporting & Identification Prescription Tracking System.

Table 3 Metrics for overall acceptability

Measure	Description	Target
Recruitment/refusal rates	Proportion of potential enrollees who were approached for recruitment but decided not to enrol.	N/A
Retention	Proportion of participants who completed ≥75% of surveys and assessments at the end of the postintervention phase, categorised as a binary outcome (Y/N).	≥75%
Adherence	Proportion of participants who completed intervention per study protocol.	≥75%
Acceptability	Median value from postintervention survey question asking whether participants would recommend VRAGI to another participant on a scale from 0 (definitely not) to 10 (definitely yes).	≥8.0

Table 4 Complete schedule of assessment

	Prescreening	Screening	Group assignment	Intervention				Postintervention
Day	−21 to −15	−14 to −8	−7 to 0	1	8	15	22	43
Informed consent	X							
Inclusion/exclusion criteria	X							
Patient demographics and clinical status (EMR dataset)	X							
Opioid prescription data (SCRIPTs and EMR)	X			X		X	X	X
Opioid diary review	X			X	X	X	X	X
Charlson Comorbidity Index([55 56])	X							
Edmonton Symptom Assessment Scale (ESAS)[54] *		X		X	X	X	X	X
Brief Pain Inventory (BPI)[53] *†		X		X	X	X	X	X
Client Satisfaction Questionnaire (CSQ)					X	X	X	X
VR Questionnaire (VRQ)					X	X	X	
Event assessment reporting				X	X	X	X	
Pre/Post Intervention Numerical Pain, anxiety, depression scale‡				X	X	X	X	X

*EMR dataset: to be completed on days 1, 2, 3 and 4 of screening week.
†All assessments must be performed post-VR session and within the visit specified windows, unless otherwise described. Additional unscheduled safety and efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of events.
‡To be completed daily, before and after VR sessions from day 1 through day 22.
AE, adverse event; EMR, Electronic Medical Record; SAE, serious adverse event; SCRIPTS, South Carolina Reporting & Identification Prescription Tracking System; UP, unanticipated problem; VR, virtual reality.

two outcomes being a composite of the four pain items to determine mean pain severity and a mean of seven daily activities to determine pain interference.[52] The BPI was created specifically to assess pain in patients with cancer and has been used in many clinical settings.[52] It has been found to be both reliable and valid across a multitude of diverse cultures and languages and used in both clinical and research settings to evaluate pain.[53]

The Edmonton Symptom Assessment Scale (ESAS) is a nine-item patient-rated symptom visual analogue scale developed for use in assessing the symptoms of patients receiving palliative care.[54] This ESAS will be used to collect information about the patients about their pain, anxiety and depression levels using a 10-point scale (ie, 0=none to 10=worst possible). The ESAS is a validated instrument for assessing symptom intensity in this study's population of people with cancer diagnoses.[54]

We designed the Client Satisfaction Questionnaire for this study. It asks three questions on a 10-point scale concerning their emotional experience and enjoyment participants had during the VR experience. The three items are scored from 0 to 10 (0=none to 10=most possible). The total score is created by summing responses with the total possible score ranging from 0 to 30.

We constructed the VR Questionnaire for direct feedback for this study. It asks three questions of the participants on a 10-point scale regarding their physical/bodily experience while using VR, such as experiencing dizziness or nausea. Items are scored from 0 to 10 (0=none to 10=most possible). The total scores are created by summing responses, and the total possible score ranges from 0 to 30.

The Morphine Milligram Equivalents (MMEs) will be measured to help calculate the total daily dose of opioids. The Opioid Diary and the SCRIPTS (South Carolina Reporting & Identification Prescription Tracking System) database will be utilised to calculate the MMEs/day for each participant across the different study arms. The South Carolina prescription monitoring programme (SCRIPTS) is intended to improve the state's ability to identify and stop diversion of prescription drugs in an efficient and cost-effective manner that will not impede the appropriate medical utilisation of licit controlled substances where there is a valid prescriber–patient or pharmacist–patient relationship. At enrolment, patients will be instructed to maintain an Opioid Diary where they will write down the number of opioid doses they used during a day. They will be instructed to maintain this for the duration of the study. The frequency of when the SCRIPTS database and Opioid Diary will be reviewed can be found in table 4, schedule of assessments.

The Charlson Comorbidity Index (CCI) was developed to predict mortality when multiple chronic conditions existed within a patient. The CCI is an algorithm composed of more than 30 comorbid chronic conditions that allow researchers and physicians to predict mortality of a patient. The CCI has shown to be valid and reliable in clinical settings and specifically for patients with cancer.[55 56]

We designed a Pre/Post Intervention Numerical Scale that will have participants provide a score from an 11-point numerical scale regarding their pain, anxiety, and depression, immediately before and after each daily session.

Prior to mailing the HMD to the next participant, VR use data will be collected from the device. This includes (1) time of use of each session in seconds and the season name;(2) score from an 11-point numerical scale for pain, anxiety and depression, answered daily, immediately before and after each session; (3) total distance traversed in the VR environment during each session; total rotation of the headset during each session.

Adherence will be monitored with self-reported use in weekly surveys. If participants indicate <6 uses during the week, they will be asked to indicate the reason(s) for low adherence. All the data will be stored in encrypted REDCap software. If subjects do not complete the surveys, they will be sent up to three reminder prompts via REDCap.

Incentives

Participants will be eligible for up to US$100 in Amazon.com gift cards. A US$25 gift card will be emailed at the end of weeks 1 and 2 if they complete ≥75% of surveys during each of those weeks. The third US$25 gift card will be emailed if they complete ≥75% of surveys and initiate the HMD return after week 3 of the intervention phase. The remaining US$25 gift card will be sent at the end of the 6-week period if they complete ≥75% of the surveys at the end of the postintervention phase.

Monitoring plan

Study progress and safety will be reviewed monthly. Progress reports, including participant recruitment and adverse events (AEs), will be provided to the monitoring committee following each monthly review. An annual report will be compiled and include a list and summary of any AEs in addition to addressing: (1) whether AE rates were consistent with prestudy assumptions; (2) reasons for dropouts; (3) whether study continuation is justified; and (4) conditions whereby the study might be terminated prematurely. The annual report will be sent to the monitoring committee and will be forwarded to the Institutional Review Board (IRB). The IRB and other applicable recipients will review study progress annually. The PI will also be sent copies of signed recommendations and comments from the monitoring committee.

Analysis

The statistical analysis will be conducted using the R software package. Statisticians will be blinded and conduct analyses based on the labelling of the four groups as 1–4. We will use intent-to-treat analysis and account for missing data if needed using multiple imputation methods if data satisfy missing-at-random assumptions. To evaluate the acceptability of this approach, we will analyse weekly

trends in usage based on user feedback from the client satisfaction questionnaire and provide ongoing technical assistance to participants to minimise attrition. We will then use a difference-in-differences (DID) approach to identify a causal effect due to the intervention on the various outcome measures. The DID approach traces the causal effect of the intervention by identifying the difference in slopes between groups postintervention, based on multiple linear regression.[57] This approach is extended to our study with four groups, where treatment effects are in the presence of other confounders and where there is more than a one-time point of interest (repeated measures data). Typically, these extensions result in a generalised hierarchical regression modelling framework with potential mixed effects and interaction effects. In our study, we use this generalised regression framework to test for a statistically significant causal effect of the intervention on each outcome. Normality will be tested by visually examining histograms and Q–Q plots of regression residuals. We will report the main effects, interaction effects, standard errors and 95% CIs on all the regression coefficients, including variance in the random effects. We expect regression coefficients for the main effects will be statistically significant. If this is the case, we will conduct post hoc tests for interaction effects between factors. Subgroup analysis will also be completed to account for possible moderation effects by sex, age, compliance, VR familiarity, comorbidities and other sociodemographic characteristics. Two-sided p values of <0.05 will be considered statistically significant.

Patient and public involvement

This protocol was developed in partnership with the University of South Carolina Patient Engagement Studio (PES). PES provided input during and beyond protocol development, such as survey and intervention burden, with the research team. The PES also helped design surveys. The PES brings together patients, community stakeholders, physicians and researchers to produce meaningful and innovative research. The studio is committed to community impact by developing an intervention for the inclusion of patients and community members with guidance from the Patient-Centered Outcomes Research Institute.

Ethics and dissemination

The study has been approved by the Prisma Health IRB (Pro00114598). All participants enrolled in the study will provide written informed consent, which includes the data sharing plan. No post-trial care is planned. Results will be disseminated in peer-reviewed scientific journals. The recruiting providers and participants will be emailed the results. Authorship eligibility is based on significant contributions to the study and review of the manuscript. The principal investigator and coinvestigators will have access to the final dataset. The protocol has been published on clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT05348174). The project is scheduled to launch recruitment at Prisma Health, SC, in November 2022. After the implementation of the intervention, data collection and statistical analysis, we expect that the results of the trial will be submitted to a peer-reviewed journal in December 2023.

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REFERENCES

1 Understanding advanced and metastatic cancer [Internet].. Cancer.org.. Available: https://amp.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html
2 van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, *et al*. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437–49.
3 Te Boveldt N, Vernooij-Dassen M, Burger N, *et al*. Pain and its interference with daily activities in medical oncology outpatients. *Pain Physician* 2013;16:379–89.
4 Rodriguez C, Ji M, Wang H-L, *et al*. Cancer pain and quality of life. *J Hosp Palliat Nurs* 2019;21:116–23 https://www.ncbi.nlm.nih.gov/pubmed/30829932
5 Temel JS, Greer JA, Muzikansky A, *et al*. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733–42.
6 Zimmermann C, Swami N, Krzyzanowska M, *et al*. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014;383:1721–30.
7 Bakitas M, Lyons KD, Hegel MT, *et al*. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the project enable II randomized controlled trial. *JAMA* 2009;302:741–9.
8 Raja SN, Carr DB, Cohen M, *et al*. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. *Pain* 2020;161:1976–82.
9 Solvik E, Ytrehus S, Utne I, *et al*. Pain, fatigue, anxiety and depression in older home-dwelling people with cancer. *Nurs Open* 2020;7:430–8 https://www.ncbi.nlm.nih.gov/pubmed/31871728
10 Deng GE, Rausch SM, Jones LW, *et al*. Complementary therapies and integrative medicine in lung cancer: diagnosis and management of lung cancer, 3rd ED: American College of chest physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e420S–36.
11 Greenlee H, DuPont-Reyes MJ, Balneaves LG, *et al*. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin* 2017;67:194–232.
12 Lyman GH, Greenlee H, Bohlke K, *et al*. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. *J Clin Oncol* 2018;36:2647–55.
13 Quigley C. Opioids in people with cancer-related pain. *BMJ Clin Evid* 2008;2008:2408.
14 Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA* 2016;315:1624–45.
15 NCCN. Treatment by cancer type. NCCN. Available: https://www.nccn.org/guidelines/category_1. Published 202AD. [Accessed January 26, 2022].
16 NCCN.. Adult cancer pain, version 3.2019, NCCN clinical practice . NCCNPublished 2022. Available: https://jnccn.org/view/journals/jnccn/17/8/article-p977.xml [Accessed January 26, 2022].
17 Lee R. *Guided imagery as supportive therapy in cancer treatment. Relias Media - Continuing Medical Education Publishing*, 1999. https://www.reliasmedia.com/articles/41900-guided-imagery-as-supportive-therapy-in-cancer-treatment
18 Kwekkeboom KL, Wanta B, Bumpus M. Individual difference variables and the effects of progressive muscle relaxation and analgesic imagery interventions on cancer pain. *J Pain Symptom Manage* 2008;36:604–15.
19 Forward JB, Greuter NE, Crisall SJ, *et al*. Effect of Structured Touch and Guided Imagery for Pain and Anxiety in Elective Joint Replacement Patients--A Randomized Controlled Trial: M-TIJRP. *Perm J* 2015;19:18–28 https://www.ncbi.nlm.nih.gov/pubmed/26222093
20 Tusek DL, Church JM, Strong SA, *et al*. Guided imagery: a significant advance in the care of patients undergoing elective colorectal surgery. *Dis Colon Rectum* 1997;40:172–8 https://dx.doi.org/10.1007/BF02054983
21 Mohammad J, Batool T. Om SRR Kambiz B. guided imagery: reducing anxiety, depression, and selected side effects associated with chemotherapy. *Oncology Nursing Forum* 2019;23.
22 Coelho A, Parola V, Sandgren A, *et al*. Kolcaba K Apóstolo J. The effects of guided imagery on comfort in palliative care. *Journal of Hospice & Palliative Nursing* 2018;20:392–9.
23 De Paolis G, Naccarato A, Cibelli F, *et al*. The effectiveness of progressive muscle relaxation and interactive guided imagery as a pain-reducing intervention in advanced cancer patients: a multicentre randomised controlled non-pharmacological trial. *Complement Ther Clin Pract* 2019;34:280–7 https://www.ncbi.nlm.nih.gov/pubmed/30712739
24 Baños RM, Espinoza M, García-Palacios A, *et al*. A positive psychological intervention using virtual reality for patients with advanced cancer in a hospital setting: a pilot study to assess feasibility. *Support Care Cancer* 2013;21:263–70.
25 Hoffman AJ, Brintnall RA, Brown JK, *et al*. Virtual reality bringing a new reality to postthoracotomy lung cancer patients via a home-based exercise intervention targeting fatigue while undergoing adjuvant treatment. *Cancer Nurs* 2014;37:23–33.
26 Zeng Y, Zhang J-E, Cheng ASK, *et al*. Meta-Analysis of the efficacy of virtual Reality-Based interventions in cancer-related symptom management. *Integr Cancer Ther* 2019 ;;18:1534735419871108.
27 Glennon C, McElroy SF, Connelly LM, *et al*. Use of virtual reality to distract from pain and anxiety. *Oncol Nurs Forum* 2018;45:545–52.
28 Bani Mohammad E, Ahmad M. Virtual reality as a distraction technique for pain and anxiety among patients with breast cancer: a randomized control trial. *Palliat Support Care* 2019;17:1–6.
29 House G, Burdea G, Grampurohit N, *et al*. A feasibility study to determine the benefits of upper extremity virtual rehabilitation therapy for coping with chronic pain post-cancer surgery. *Br J Pain* 2016;10:186–97.
30 Tsuda K, Sudo K, Goto G, *et al*. A feasibility study of virtual reality exercise in elderly patients with hematologic malignancies receiving chemotherapy. *Intern Med* 2016;55:347–52.
31 Niki K, Okamoto Y, Maeda I, *et al*. A novel palliative care approach using virtual reality for improving various symptoms of terminal cancer patients: a preliminary prospective, multicenter study.. *J Palliat Med* 2019;22:702–7.
32 Rutkowski S, Czech O, Wrzeciono A, *et al*. Virtual reality as a chemotherapy support in treatment of anxiety and fatigue in patients with cancer: a systematic review and meta-analysis and future research directions. *Complement Ther Med* 2021;61:102767.
33 Austin PD, Siddall PJ, Lovell MR. Feasibility and acceptability of virtual reality for cancer pain in people receiving palliative care: a randomised cross-over study. *Support Care Cancer* 2022;30:1–11.
34 Chirico A, Maiorano P, Indovina P, *et al*. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. *J Cell Physiol* 2020;235:5353–62 https://www.ncbi.nlm.nih.gov/pubmed/31957873
35 Sacks OA, Barnato AE, Skinner JS, *et al*. Elevated risk of COVID-19 infection for hospital-based health care providers. *J Gen Intern Med* 2021;36:3642–3 https://www.ncbi.nlm.nih.gov/pubmed/34405347
36 Burhenn P, Olausson J, Villegas G, *et al*. Guided imagery for pain control. *Clin J Oncol Nurs* 2014;18:501–3.
37 Nooner AK, Dwyer K, DeShea L, *et al*. Using relaxation and guided imagery to address pain, fatigue, and sleep disturbances: a pilot study. *Clin J Oncol Nurs* 2016;20:547–52.
38 Becker WC, Dorflinger L, Edmond SN, *et al*. Barriers and facilitators to use of non-pharmacological treatments in chronic pain.. *BMC Fam Pract*.;2017:41.
39 Schulz-Stübner S, Krings T, Meister IG, *et al*. Clinical hypnosis modulates functional magnetic resonance imaging signal intensities and pain perception in a thermal stimulation paradigm. *Reg Anesth Pain Med* 2004;29:549-–56.
40 Del Casale A, Ferracuti S, Rapinesi C, *et al*. Pain perception and hypnosis: findings from recent functional neuroimaging studies. *Int J Clin Exp Hypn* 2015;63:144–70 https://www.ncbi.nlm.nih.gov/pubmed/25719519
41 De Pascalis V, Varriale V, Cacace I. Pain modulation in waking and hypnosis in women: event-related potentials and sources of cortical activity. *PLoS One* 2015;10:e0128474 https://www.ncbi.nlm.nih.gov/pubmed/26030417
42 Kerr CE, Sacchet MD, Lazar SW, Sacchet MD, *et al*. Mindfulness starts with the body: somatosensory attention and top-down modulation of cortical alpha rhythms in mindfulness meditation. *Front Hum Neurosci* 2013;7:12 https://www.ncbi.nlm.nih.gov/pubmed/23408771
43 Garmon B, Philbrick J, Becker D, *et al*. Mindfulness-based stress reduction for chronic pain: a systematic review. *Journal of Pain Management* 2014;7:23–6.

44 Berna C, Leknes S, Ahmad AH, *et al*. Opioid-Independent and opioid-mediated modes of pain modulation. *J Neurosci* 2018;38:9047–58 https://www.ncbi.nlm.nih.gov/pubmed/30201765
45 Kenney MP milling LS. The effectiveness of virtual reality distraction for reducing pain: a meta-analysis. *Psychol Conscious* 2016;3:199–210.
46 Faul F, Erdfelder E, Buchner A, *et al*. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–60.
47 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*;2013:e7586.
48 Arshad I, De Mello P, Ender M, *et al*. Reducing Cybersickness in 360-Degree virtual reality. *Multisens Res* 2021;35:1–17.
49 FAQ - CleanBox technology [Internet]. CleanBox technology, 2021. Available: https://cleanboxtech.com/faq/
50 Cleanbox CX1 [Internet]. CleanBox technology, 2022. Available: https://cleanboxtech.com/product/cleanbox-cx1-uvc-led-vr-headset-cleaner/
51 de Borja M-T, Chow E, Bovett G, *et al*. The correlation among patients and health care professionals in assessing functional status using the Karnofsky and eastern cooperative Oncology Group performance status scales. *Support Cancer Ther* 2004;2:59–63.
52 Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap* 1994;23:129–38.
53 Kumar SP. Utilization of brief pain inventory as an assessment tool for pain in patients with cancer: a focused review. *Indian J Palliat Care* 2011;17:108–15.
54 Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton symptom assessment scale. *Cancer* 2000;88:2164–71.
55 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classification of prognostic comorbidity for longitudinal studies: development and validation. *J Chron Disease* 1987;40:373–83.
56 Hall WH, Ramachandran R, Narayan S, *et al*. An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer* 2004;4:94.
57 Dimick JB, Ryan AM. Methods for evaluating changes in health care policy: the difference-in-differences approach. *JAMA* 2014;312:2401.