An Immersive Virtual Reality Intervention for Preoperative Anxiety and Distress Among Adults Undergoing Oncological Surgery: Protocol for a 3-Phase Development and Feasibility Trial

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Submitted to: JMIR Research Protocols
on: December 21, 2023

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Abstract

Background: Preoperative state anxiety (PSA) is distress and anxiety directly associated to perioperative events. PSA is associated with negative postoperative outcomes like longer hospital length of stay, increased pain, higher opioid use, and higher rates of re-hospitalization. Psychological prehabilitation such as education, exposure to hospital environments, and relaxation, has been shown to mitigate PSA, however there are limited skilled personnel in clinical practice. Immersive virtual reality (VR) has the potential for greater accessibility and enhanced integration into an immersive and interactive virtual experience. VR is rarely used in the preoperative setting, but similar forms of stress inoculation training involving exposure to stressful events have improved subjects' psychological preparation in contexts such as military deployment. This study seeks to develop and investigate a targeted PSA intervention in patients undergoing an oncologic surgical procedure using a single preoperative exposure to a VR program.

Objective: The primary objectives are (i) to develop a novel VR program for patients undergoing oncological surgery with general anesthesia, (ii) to assess the feasibility and acceptability of a single exposure to this intervention in the preoperative period, (iii) to assess the feasibility and acceptability of outcomes measures of perioperative anxiety and distress and (iv) to use these results to refine the VR content and outcome measures for a larger trial of the VR exposure. A secondary objective is to preliminarily assess the clinical utility of the intervention for PSA.

Methods: This study comprises 3 phases. Phase 1 (completed) involved the development of a VR prototype targeting PSA, using multidisciplinary iterative input. Phase 2 (ongoing) involves examining the feasibility aspects of the VR intervention. This randomized feasibility trial involves assessing the novel VR preoperative intervention compared to a control VR condition and

treatment as usual group among breast cancer surgery patients. Phase 3 will involve refining of the prototype based on feasibility findings and input from people with lived experience for a future clinical trial, employing focus groups with participants from Phase 2.

Results: This study was funded in March 2019. Phase 1 was completed in April 2020. Phase 2 is currently underway and data collection will be completed in January 2024. Focus groups will also be completed in January 2024. Both the feasibility study and focus groups will contribute to further refinement of the initial VR prototype (Phase 3) in Winter of 2023/2024.

Conclusions: The findings from this initiative will contribute to the limited body of research examining feasible and broadly accessible interventions for PSA. Knowledge gained from this research will contribute to the final development of a novel VR intervention to be tested in a large population of oncological patients prior to surgery in a randomized clinical trial. Clinical Trial: ClinicalTrials.gov NCT04544618 (Phase 2 only)

(JMIR Preprints 21/12/2023:55692)
DOI: https://doi.org/10.2196/preprints.55692

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Abstract

Background: Preoperative state anxiety (PSA) is distress and anxiety directly associated to perioperative events. PSA is associated with negative postoperative outcomes like longer hospital length of stay, increased pain, higher opioid use, and higher rates of re-hospitalization. Psychological prehabilitation such as education, exposure to hospital environments, and relaxation, has been shown to mitigate PSA, however there are limited skilled personnel in clinical practice. Immersive virtual

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Conclusions: The findings from this initiative will contribute to the limited body of research examining feasible and broadly accessible interventions for PSA. Knowledge gained from this research will contribute to the final development of a novel VR intervention to be tested in a large population of oncological patients prior to surgery in a randomized clinical trial.

Trial Registration: ClinicalTrials.gov NCT04544618 (Phase 2 only)

Keywords: virtual reality; pre-operative anxiety and distress; perioperative mental health; breast cancer; oncological surgery

Introduction

Background

There is increasing recognition of the detrimental effects of anxiety and distress in medical populations. The National Comprehensive Cancer Network (NCCN) has advocated for psychological distress to be the sixth vital sign[1]. Both the aging demographic and overall population is increasing

in Canada, which confers an elevation in overall cases of cancer and those requiring surgery [2]. The patients lived experience of anxiety and distress before surgery is a near universal, and often an overlooked aspect of the perioperative journey. In a study of over 15,000 patients undergoing non-obstetric surgery in the United Kingdom, anxiety was rated by patients as the *worst* aspect of the perioperative experience [3]. Preoperative anxiety and distress have been shown to significantly affect negative perioperative outcomes (e.g., increased hospital length of stay, pain, opioid use, and re-hospitalization) [4]. However, few feasible preoperative interventions exist to mitigate preoperative anxiety and distress, termed preoperative state anxiety (PSA) throughout [5].

Preoperative State Anxiety (PSA)

Rates of psychiatric disorders (e.g., anxiety disorders, depression) are elevated across surgical samples, with particularly high rates among breast cancer surgery patients [6]. These psychiatric disorders are associated with a range of poor postoperative health outcomes [7] including, increased mortality [8], [9]. The presence of a psychiatric disorder preoperatively is also associated with significantly greater healthcare costs incurred among breast cancer surgery patients [6]. A history of psychiatric disorders also increases the risk of acute PSA in elective surgery [10] although PSA can also occur outside the context of threshold psychiatric disorders. PSA is defined by anticipatory distress or anxiety related specifically to perioperative factors such as pain, loss of independence, the surgery itself, anesthesia, and/or death, [11], [12] but can also relate to unfamiliar environments, such as the operating room (OR) and/or encounters with health professionals [13], [14]. PSA tends to be transient in nature based on a present stressor (e.g., upcoming surgery), however, can be clinically significant and debilitating in around 40% of surgical patients [15]. PSA is often impacted by unfamiliarity and uncertainty regarding the surgical process [16]. Research by our group and others [12], [14] demonstrates that PSA relates to several OR environmental stimuli including exposure to and placement of the anaesthetic face mask, intravenous cannula insertion, limb restraint application and inadequate information about the intraoperative process across surgical groups. Patients undergoing oncologic surgery experience elevated rates of preoperative distress, ranging from 23-77% in recent research [17], [18], [19]. PSA in this population has been found to relate to uncertainties of what the surgeon might find and/or operative procedures, or regarding the effects of surgery itself [10]. Oncologic surgery patients' experiences with PSA have been associated with increased postoperative pain, nausea, discomfort, fatigue, and analgesic consumption [10], [11], [12], [13], [14] highlighting its significance, and raising the question of whether reducing PSA can impact postoperative outcomes.

Interventions Targeting PSA

It is well understood that psychological states and disorders are highly responsive to a range of empirically supported, targeted psychological/behavioral treatments. In light of this, there is a growing body of literature examining preoperative psychological interventions to reduce negative postoperative sequelae, with some promising, but mixed, results. A Cochrane review by Powell and colleagues [20], examined the evidence on psychological preparation prior to surgery using general anesthesia on a range of postoperative outcomes. These authors concluded that there were significant positive effects for a range of interventions but overall, the quality of evidence was low, which in part related to the heterogeneity of the data and employed methodologies. The interventions with the most empirical support across a range of outcomes utilized relaxation preoperatively. In oncological surgeries specifically, systematic reviews have demonstrated that preoperative psychological interventions are associated with improved outcomes, particularly patient reported outcomes such as mood and anxiety, quality of life, fatigue, and somatic symptoms [21], [22]. However, many psychological interventions, such as cognitive behavioral therapies, are high-resource approaches

requiring expert administration and not feasibly implemented for the large and growing number of surgical interventions. This is particularly true in publicly funded, and often (already) overwhelmed healthcare systems. Although digital technology options have addressed some of these challenges (e.g., cost and accessibility), these tend to be focused on more general cognitive behavioral therapy. Formal mobile-based cognitive behavioural therapy interventions still require greater and longer patient engagement and often mental health professional support [23]. Additionally, cognitive behavioural therapy is most often employed to address trait anxiety or mental disorder symptomatology by dealing with maladaptive thoughts and behaviours over time [24], rather than the more transient nature of PSA, which is a psychological state directly related to the stressor [25]. Thus, VR may be optimally suited to address PSA as it requires less time commitment and may be undergone at any point in the weeks leading up to surgery providing greater flexibility. The VR technology can reduce the need for direct healthcare provider support and has the potential for at home use.

The vast majority of existing studies examining non-behavioral interventions for PSA have focused on preoperative education with mixed and often smaller effect sizes [26]. Educational interventions typically take the form of patient reading material (e.g., informational brochures), which are often underutilized, lack important information, are provider rather than patient-directed, and require a higher level of health literacy [26]. Successful educational initiatives for mitigating PSA, which also translate to decreased perioperative pain and increased functioning, often include poorly feasible, high-resource initiatives such as preoperative classes led by anesthesiologists and surgeons [27]. Researchers have also examined the impact of enabling patients to tour the OR prior to surgery on levels of PSA [28], since the OR environment is an anxiety-inducing trigger for surgical patients [12], [13], [29]. Although this approach has been associated with reductions in levels of PSA [28], it has limited feasibility to be administered broadly due to the infrequent availability of ORs and limited resources/personnel to implement this intervention. The feasibility of such an approach is even further reduced in the context of COVID-19, and future pandemics, where hospital accessibility is restricted and maintaining sterility in patient areas such as the OR is of utmost importance.

With respect to the use of medications for PSA, the use of anxiolytics preoperatively is a somewhat controversial practice. A survey of 3661 anesthesiologists from the American Society of Anesthesiologists (ASA) was conducted to determine whether anesthesiologists ask their adult patients about preoperative anxiety and what methods they utilize to reduce it [30]. They found that over 60% of anesthesiologists reported asking their patients about anxiety and that 91.6% of these anesthesiologists prescribed anxiety medication, most commonly, the benzodiazepine Midazolam [30]. In the preoperative environment benzodiazepines may be used for relaxation, sedation, ease of administering anesthesia, or to suppress seizure activity. Although there are reasons for use of benzodiazepines outside of PSA, they are not without risk and not ideal in all populations. Specifically, benzodiazepines can be associated with adverse outcomes such as impaired motor and cognitive functioning, delirium, and respiratory depression [31]. Benzodiazepines are also not recommended for use in older adults over 65 years as they are at increased risk for cognitive impairment and delirium [31]. Furthermore, the use of benzodiazepines for anxiety reduction in the acute pre-operative period is not associated with any differences in patient satisfaction as assessed on the day after surgery, suggesting the lack of clinical benefit for patients [32]. Other anxiolytics, such as selective serotonin reuptake inhibitors (SSRI's), are not suitable for PSA and are more commonly prescribed for chronic mental disorders. Pharmacological interventions also do not target the cause of anxiety experienced by patients prior to surgery, such as lack of perioperative information, and fear of the OR environment, nor do they use foundational exposure (i.e., exposing patients to a feared environment to reduce avoidance and promote habituation), and relaxation paradigms proven to be effective for PSA in other contexts.

Virtual Reality (VR)

VR is a computer-generated three-dimensional environment in which a user may be immersed through visualization and interactions. VR can be used to approximate reality in order to achieve ecological validity for a targeted environment and can yield affective responses [33]. VR represents a potentially novel targeted modality for PSA because it enables the integration of several effective intervention techniques such as exposure to hospital environments, education, and relaxation strategies. VR interventions have been shown to significantly reduce anxiety and other psychiatric symptoms in other contexts (e.g., fear of flying, injection phobia, fear of heights), and are used as a pre-deployment prehabilitative intervention to prepare military personnel for anticipated exposure to acute stress during combat (i.e., stress inoculation training; [34]). Evidence suggests prehabilitative VR interventions may be associated with reductions in psychological distress, both pre- [35], [36] and post- [37] deployment. Recently, researchers have evaluated whether preoperative VR simulations that expose patients to the OR can mitigate PSA [38], [39]. Preliminary research in paediatric populations has found that preoperative exposure in a VR simulation to the OR environment reduces PSA and increases compliance during induction of anesthesia [39] and is regarded positively and accepted by patients [40]. In recent years, some targeted VR interventions have also been developed for adult populations. Two systematic reviews by Yu et al. [41] and Mbewe and Smith [42] identified five previous studies utilizing VR to reduce perioperative anxiety in adult patients. Yu et al. [41] included studies examining both perioperative and periprocedural anxiety and eligibility criteria was limited to VR interventions focused on OR tours specifically. The interventions were all in video format with the VR experiences ranging from first [43], to third person point of views [38], [44], some of which also provided 360° visuals [45], [46]. Each intervention was meant to educate the participant on the surgical/procedural process and/or expose them to the OR environment. Results varied, with some studies reporting no differences in anxiety levels between the VR intervention and control groups, [44], [45] while others' found anxiety to be significantly decreased with the VR intervention [38], [43], [46]. Importantly, VR interventions were also found to better patients' procedural understanding, and increase patient satisfaction and preparedness [38], [46]. Mbewe and Smith [42] included 3 additional studies in their meta-analysis as they were focused on surgical cases and did not restrict VR interventions to OR tours, thus including other VR interventions (e.g., nature scenes). The alternative VR interventions included a "training" video focused on educating patients on wide ranging aspects of the surgical process [47], a 360° nature video with relaxing music and birdsong [48] and a beach scene with audio playing a muscle relaxation technique [49]. Results of their meta-analysis demonstrated VR interventions have greater positive impacts on preoperative anxiety when compared to the standard of care; however, the effect size was relatively small [42].

The impact of these VR interventions may have been limited due to lacking relevant perioperative information or exposure and only displaying re-enactments or simply exposing patients to features of the surgical process as opposed to an immersive patient-directed VR experience. Immersive patient-directed VR refers to environmental fluidity changes with head movement, which facilitates presence and immersion and deepens engagement [50]. Displaying videos offers a limited sense of presence and immersion as the user cannot directly interact with the environment, and therefore ecological validity is reduced [51]. The importance of immersion and interactivity on agency and embodied learning has been supported in prior research [52]. For example, when using VR exposure to treat anxiety disorders, first-person body experiences, and other features that enhance immersion such as movement tracking and audio/tactile exposure have been found to be important components of effective VR interventions [53]. A sense of immersion is not only positively related to feelings of anxiety (which is a necessary component of exposure-based paradigms) but may also enhance the

effectiveness of the intervention in facilitating behavioural change [53], [54]. In addition, the immersive aspect of VR is biologically supported with studies demonstrating that immersing patients in a stressful VR environment can alter biomarkers of stress [55]. This initial research is promising and provides preliminary support for the utility of immersive VR to mitigate PSA and ultimately may improve perioperative outcomes. However, one way in which this body of literature is limited is very few, if any, studies have examined the feasibility of these types of interventions, which is a critical step given its novelty in the perioperative setting.

Study Overview and Objectives

Based on these gaps in the literature and the importance of developing practically implemented, low-resource interventions for PSA, we designed and are evaluating the feasibility of a novel immersive VR intervention, first targeting PSA among breast cancer surgery patients. Cancer surgery patients were identified as the first target group given their high rates of PSA [17], [18], [19] and the large volume of cases (nearly 50% of cancer patients undergo surgery), which are scheduled as elective surgeries. The use of VR is particularly advantageous for elective procedures given that it provides the opportunity for preoperative interventions in the weeks before surgery. The development of the intervention is an iterative, collaborative process using multidisciplinary health professional input and later employing focus groups of patients with lived experience. The use of both qualitative and quantitative methods promotes our ability to hear the patient voice and to make relevant adaptations to the application as directed by our analysis based on feasibility and focus group findings. This will be achieved in three phases as depicted in Figure 1, developed in line with international guidelines established by the VR-CORE committee for VR trials in healthcare [56]. Phase 1 (completed; in line with VR-CORE guideline's framework VR1 phase) involved the development of an initial VR prototype that was developed in conjunction with healthcare professionals working in the OR and engineers (authors MS, CP, VGS) at the National Research Council of Canada [57]. This prototype comprises an immersive virtual representation of the OR and patient induction process for an individual undergoing breast cancer surgery with general anesthesia. Phase 2 (underway; in line with VR-CORE guideline's framework VR2 phase) uses a randomized design (VR intervention vs. VR control [i.e., nature trek] vs. treatment as usual, TAU) to assess feasibility on a sample of breast cancer surgery patients. The feasibility study used quantitative scales to understand the recruitment and randomization capability, acceptability, and feasibility of the study design along with preliminary utility for reducing PSA. In Phase 3 (underway; also in line VR-CORE guideline's framework VR1 phase, as we are collecting user-testing feedback to improve content of VR), we are conducting focus groups with select participants from the feasibility trial, and results based on the focus groups along with the feasibility findings will inform continued refinements of the prototype for a future randomized clinical trial (in line with VR-CORE guideline's framework VR3 phase). An effective PSA-reducing intervention has the potential to mitigate poor perioperative mental and physical health outcomes in oncological surgery patients and have significant cost savings for the overall healthcare system. An initial successful VR platform could be modified and applied to other surgical populations in the future.

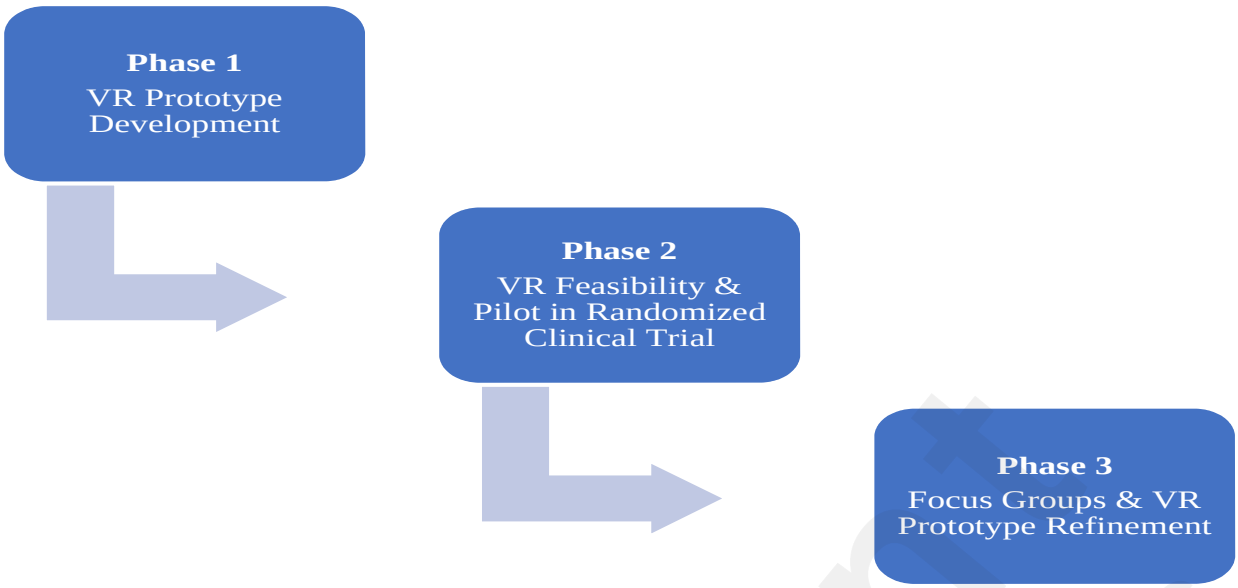

Figure 1. Flowchart of the three-phase development.

Methods

Phase 1 (complete)

VR Development

Phase 1 involved the development of the initial VR prototype, developed in the Unity Game Engine (Unity Technologies) and deployed using the Oculus Rift S headset. No patient participants were involved in this component of the research, therefore ethical approval was not required. We aimed to develop the initial VR prototype to virtually replicate an OR and simulated anesthetic induction at the Health Sciences Centre (HSC) in Winnipeg, Manitoba, a tertiary care, university affiliated hospital connected to a provincially mandated cancer agency. With institutional approval, several photographs and videos were taken of the OR. Further, with signed patient consent, one live induction process was audio and video recorded (which excluded any visual of the patient). Further, an e-mail was sent to all attending anesthesiologists at the HSC requesting for them to provide their standard patient “induction and safety scripts”. We received four scripts which were compared and consistent elements across scripts were amalgamated into a “standard script” to be integrated into the VR simulation.

An iterative and collaborative development process was employed to create the VR environment and simulation. The initial prototype was based on all elements included in an induction sequence on a real patient, which was filmed. Based on input and feedback from co-authors and OR professionals at the HSC in addition to consultations between co-authors and the VR development team at the National Research Council, further elements to be implemented (equipment, personnel, narrations, animations, etc.) were identified and prototypes developed. In the interest of having a prototype to test in a timely manner and to reserve the bulk of the grant funds to commit to the development of the intervention following patient feedback via the feasibility and focus groups, specific decisions were made to animate aspects in the operating room that have been reported by patients to be the most anxiety provoking [14]. Prototypes were trialed regularly by co-authors and feedback incorporated in the next round of refinement. Phase 1 commenced in November 2019 and was

completed by April 2020 (see Figure 2 for screenshots of the immersive VR OR environment and Figure 3 for the administration set-up). A manuscript detailing the technical aspects of the VR creation is in development.

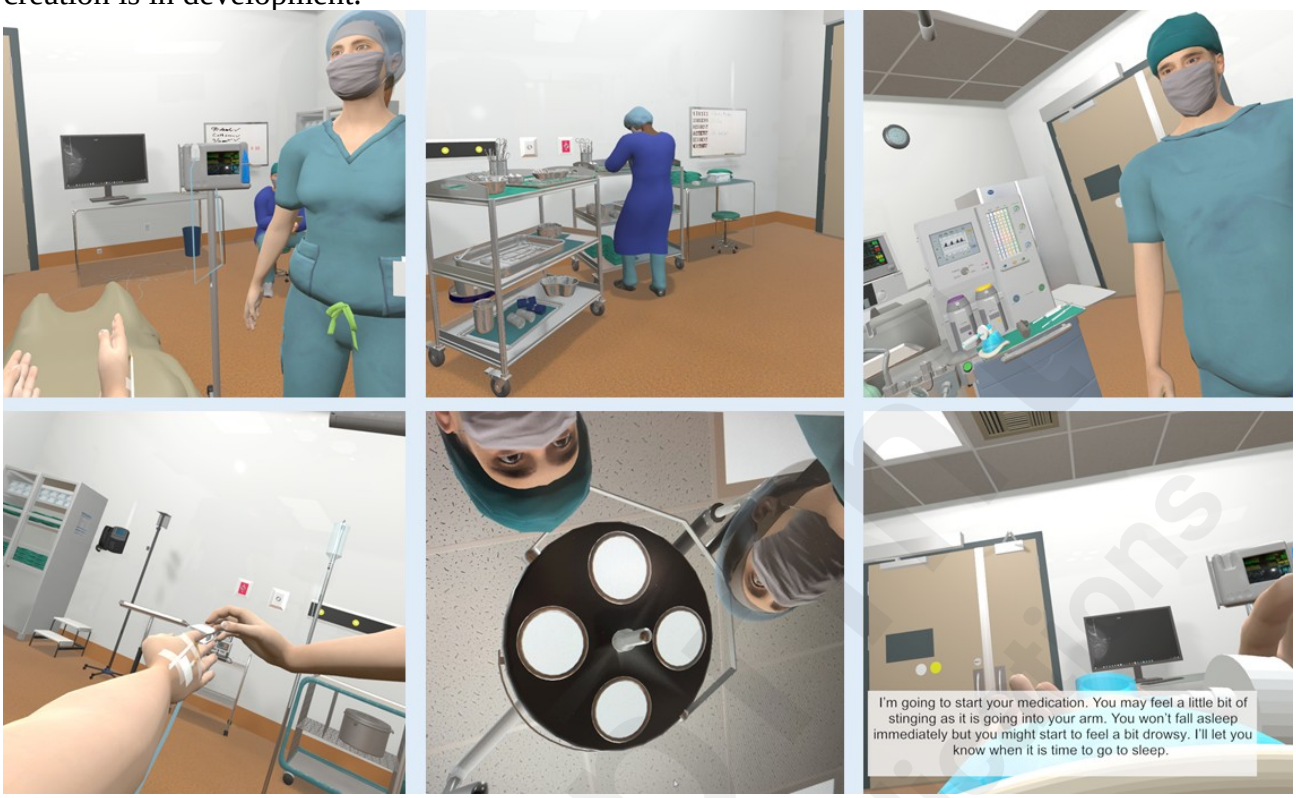

Figure 2. Screenshots of the immersive virtual reality operating room environment.

Figure 3. Virtual reality administration and set-up.

Components of the Initial VR Prototype

The user starts the simulation seated on a virtual operating table in the OR. The user is provided a

minimum duration of five minutes to visually “explore” the environment, which includes surgical (e.g., instruments, lights, medical devices, sterile items, x-ray) and anesthetic (e.g., medications, anesthetic monitors) items. The environment also includes background noises (e.g., a beeping monitor), and lighting consistent with the OR environment. Several healthcare personnel (i.e., an anesthetist, surgeon, and two nurses), including a woman and person of color are also present in the room. Following at least five minutes of exploration, an induction narrative simulation commences. The patient is instructed to lie supine (on the virtual OR table) and is taken through a mock anesthetic induction process from a first-person perspective. For the initial prototype the patient’s avatar was developed as white and gender neutral. One of the virtual nurses and the virtual anesthetist speak to the patient and walk them through the steps while the procedures are being performed. The narrative component includes attaching electrocardiogram stickers, attaching a pulse oximeter, completing a safety briefing, and placing an oxygen mask over the patient’s face. The additional steps of attaching a blood pressure cuff, attaching an intravenous line to the cannula on the hand and injection of antibiotics and anesthesia are described but not animated in the VR. As mentioned above, the animation of these steps was not included due to time and funding constraints, along with the desire of having the final simulation (including the animated components) be patient-informed. The point in the virtual induction that the patient would be falling asleep the VR screen fades to black and the simulation ends. To further encourage immersion, the induction script includes periods of patient engagement including having the patient place their right arm correctly for the nurse and specifying their name, date of birth, type of surgery and whether they have any allergies (as would be done as part of the mandatory World Health Organization surgical safety briefing). All of this is done in real time. The OR induction process is controlled by a combination of auto-advancement when certain physical positioning requirements are detected and input from research personnel who progress the patient through each phase of information delivery and patient engagement (e.g., responding to questions). However, haptic feedback to participants was not provided, as this was beyond the scope of the study objectives, and the resources available at the time.

Phase 2 (underway)

Study Design and Ethics Approval

This study employs a single centre feasibility and pilot randomized clinical trial with three arms. The study was registered on ClinicalTrial.gov (ID: NCT04544618) on September 10, 2020 [58], and received ethical approval by the University of Manitoba Health Research Ethics Board on June 30, 2020 (HS23957). Ethical amendments were approved in January 2021, September 2021, April 2022, and November 2022 (Appendix 1).

Overview

Phase 2 assesses the feasibility and preliminary outcomes of the VR OR prototype among breast cancer surgery patients. Specifically, with respect to the feasibility of this intervention, this study evaluates: (1) recruitment capability and resulting sample characteristics, (2) data collection procedures and selecting an appropriate outcome measure of PSA, and (3) participant acceptability and suitability of the VR OR intervention (i.e., the active intervention), and the inclusion and acceptability of a VR control group (Nature Treks; i.e., a non-OR immersive VR nature environment) and a TAU group. In addition, as a final aim, this study (4) pilot tests the preliminary impact of the active intervention on PSA.

This study aims to recruit a sample consisting of 45 participants (15 randomized to each arm [i.e., active intervention, VR control, TAU]). This target sample size is consistent with recommended guidelines for determining the sample size of a pilot/feasibility study and previous studies of this nature [59], [60]. Further, as an aim of this feasibility study, we are evaluating the extent to which we are able to recruit participants within the target population, which will inform modifications to recruitment method and expected duration of the upcoming randomized controlled trial (RCT).

Inclusion and Exclusion Criteria

Eligibility for participation includes: (a) being 18 years of age or older, (b) ability to speak and read English, (c) having a breast cancer diagnosis, and (d) are scheduled/being scheduled to undergo breast cancer surgery under general anesthesia at the HSC. Those who do not meet these criteria, are not competent to provide informed consent (e.g., due to cognitive impairment), or are unable to participate in a VR intervention (e.g., due to significant visual or auditory impairments) are excluded.

Consent

Participants first give verbal consent to be contacted for research purposes after being briefly told about the study at the individual's surgical oncology appointment or at a preoperative education class. Alternatively, if learning about the study from a poster, patients contact our research team directly (as described in *Recruitment*). We obtain verbal consent over the phone from participants in the screening period and written informed consent prior to their participation in the study (via mail or email).

Recruitment

Oncological surgery patients are recruited from the HSC via posters, patient surgical oncology appointment, or preoperative education class at the Shared Health Breast Health Centre (i.e., a public health breast centre that coordinates clinical assessment, diagnostic tests, treatment, education, and support) or the Breast & Gyne Cancer Centre of Hope (i.e., resource centre). A staff person/physician at the Breast Health Centre or Breast Cancer Center of Hope (or research coordinator) briefly describes the study and interested patients' contact information are recorded. Recruitment posters with study staff's contact information are posted at the Breast Health Centre, Breast Cancer Center of Hope, the HSC, and online for any potential participants not identified at the time of their surgical oncology appointment or the preoperative education class.

Protocol

Phase 2 employed a single-blind randomized design (1:1:1 randomization; stratified according to surgery type [with vs. without reconstruction] and whether neoadjuvant chemotherapy was received; stratification enables equal proportions of participants with these characteristics across each of the three study groups), using quantitative and qualitative methodologies. These were done to assess the feasibility of and pilot the VR simulation to expose breast cancer surgery patients to the OR and induction process (i.e., VR OR), compared to a non-surgery-related VR simulation (i.e., VR control) and TAU. All participants complete self-report measures approximately 2 weeks prior to surgery (i.e., baseline; for VR groups, this will occur on the day of the VR visit, prior to and after testing the intervention), on the day of surgery (preoperative), 5 days after surgery (acute postoperative), and 30 days after surgery (30 day postoperative).

Participants are randomized during the recruitment call if they provide verbal consent to participate. Randomization is done using an online random number generator,[61] and details of how these random numbers are generated are published on the website. A master file was created in Excel by author JS, and consisted of four different stratification groups to correspond to the number of combinations that there could be (1: no chemotherapy, no reconstruction; 2: no chemotherapy, with reconstruction; 3: chemotherapy, no reconstruction, 4: chemotherapy and reconstruction). Using the online number generator, each stratification group was populated with equal portions of the randomly ordered numbers of 1, 2, or 3, which corresponded to the intervention groups a participant could be assigned to (1: OR intervention; 2: nature trek intervention, 3: treatment as usual). Only research personnel who randomized the participants had access to the file. Due to the nature of this study, only partial blinding was possible. Specifically, those in the TAU group had no VR intervention, but those randomized to VR control versus VR active intervention were blinded. Consenting individuals who express an interest in participating are either mailed or emailed a written informed consent form according to their preference. Participants randomized to either the active or VR control intervention groups schedule a meeting date to undergo the VR intervention, approximately 2 weeks prior to their surgery, during their phone call with the study coordinator. On the day of the intervention meeting, participants complete baseline questionnaires prior to the intervention, and additional questionnaires following the intervention (detailed below). Those randomized to TAU are either emailed a link to complete the baseline measures online using Qualtrics software (Qualtrics, Provost, UT, 2023), or are mailed a hard copy, depending on their preference, 2 weeks prior to their surgery. On the day of surgery, preoperatively, participants again complete the measures assessing PSA that had been assessed at baseline. Five days postoperatively, participants will complete the PSA measures, in addition to the other initial baseline measures. Finally, all baseline measures are re-administered at 30-day postoperative follow-up. For both postoperative follow-ups, participants have the option to receive hard copies of the measures via mail (to complete within 72 hours) or a survey link to complete the measures online.

For the active intervention group, the VR simulation begins with the patient sitting on a hospital bed, wearing the VR headset, and holding the controllers. The details of the final prototype are described in Phase 1 and represented in Figure 2. For the exploration component, the patient is instructed to explore the virtual OR for a minimum of 5 minutes, although the patient can explore for a longer duration (the total duration engaged in the simulation is tracked for each participant). Following the exploration period, the scripted portion of the simulation begins. As detailed above, the simulation ends after the virtual oxygen mask is placed on the patient's mouth, and the screen darkens. The scripted portion of the simulation is approximately 3 minutes long (i.e., participants will spend a minimum of 8 minutes engaged in the VR intervention).

Participants randomized to the control intervention have the opportunity to explore a non-surgery-related VR simulation, pre-programmed to the VR goggles (i.e., Nature Treks simulation). Participants are instructed to explore a selected nature environment for a minimum of 10 minutes, and their total duration engaged with the simulation is also tracked. Participants in the TAU group receive standard of care; they receive no additional intervention and have the option of receiving information at their surgical oncology appointment and attending preoperative education classes, which all patients have the opportunity to attend. Following completion of the study, all participants are provided with a debriefing form to explain the purposes of the study.

Measures

A variety of self-report measures are administered to participants across four phases of this study (i.e., baseline/VR visit, preoperative, acute postoperative, 30 days postoperative). Baseline measures

are administered approximately 2 weeks prior to surgery (at the VR intervention visit for the intervention groups, or via mail/online for the TAU group). These measures include: a background sociodemographic questionnaire (e.g., assessing age, marital status, diagnosis, type of surgery, previous history of surgeries, mental health diagnoses), Preoperative Intrusive Thoughts Inventory (PITI)[62], Amsterdam Preoperative Anxiety Information Scale (APAIS)[63], National Comprehensive Cancer Network (NCCN) Distress Thermometer (a visual analogue scale; also adapted for anxiety)[64], [65], Peritraumatic Distress Inventory (PDI)[66], Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)[67], Brief Resilient Coping Scale (BRCS)[68], and Patient Reported Outcomes Measurement Information System (PROMIS) anxiety[69], depression[69], global health[70], fatigue[71], and emotional support scales[72]. Sociodemographics collected were based off of a previous study by Grocott et al. (2023) that itself informed this research study[73]. All mental health symptom scales are empirically validated self-report measures in various health populations, languages, and cultures. During the VR simulation, we also monitor participants' skin conductance (using Mindfield® eSense Skin Response) and heart rate (using a Fitbit®) while engaged in the VR simulation; participants are asked to report their level of distress and anxiety (using the NCCN Distress/Anxiety Thermometer scale of 0-10) during the intervention (at approximately 7 minutes after beginning). Throughout the simulation, research personnel complete a standardised behavioral observation form recording any notable verbal or non-verbal indications while in the intervention. Following the simulation, the intervention groups complete the iGroup Presence Questionnaire [74] and a patient acceptability questionnaire (developed by the research team, including both closed-ended and open-ended items for participants to describe their impressions of the intervention). The patient acceptability questionnaire contains questions pertaining to rating the extent that the participant agreed to thirteen statements about the VR from 0-100% (e.g., "I found the VR intervention was helpful", "The VR intervention worsened my anxiety/concerns about my surgery", etc), open and closed questions about motion sickness, open-ended questions about what the participant liked/disliked and what they found helpful about the VR (if applicable), open and closed questions about whether the VR intervention was worthwhile, and a closed question about other elements that should be included in the VR OR simulation.

On the day of surgery, all participants are asked to complete the PITI, APAIS, and NCCN Distress/Anxiety Thermometer either while they are in the waiting room or the preoperative holding area (depending on when is most convenient and timings of surgeries). Further, we again monitor participants' skin conductance and heart rate at this time. Participants are also asked to provide an additional rating for the NCCN Distress/Anxiety Thermometer while in the OR; instead of using the paper copy in the OR, the study coordinator or anesthesiologist asks participants to verbally indicate their current level of distress and anxiety (i.e., from 0-10). Five days after surgery, participants are asked to complete the NCCN Distress/Anxiety Thermometer, PROMIS anxiety, depression, global health, fatigue, and pain intensity scales, a visual analogue anxiety/distress graph, a postoperative summary form (to capture length of hospital stay, and impressions of the various preoperative anxiety and distress measures), BRCS, and the PDI. Those in the active intervention group also receive open-ended questions requesting feedback to inform modifications that should be made to the second model of the simulation (in Phase 3). Finally, 30 days after surgery, participants are asked to complete NCCN Distress/Anxiety Thermometer, PROMIS anxiety, depression, global health, fatigue, and pain intensity scales, BRCS, and PC-PTSD-5.

As will be detailed in the feasibility manuscript, although a number of self-report and objective measurements were obtained, primary measures relate to feasibility (e.g., recruitment and dropout rate and VR impressions and feedback) and primary pilot aims identify primary measures as those assessing PSA. The primary outcome measure for the larger future clinical trial will be determined based on the current study. The proposed primary outcome measures of interest include: PITI,

APAIS, and NCCN Distress/Anxiety Thermometer. This feasibility study will also evaluate the extent to which these measures are completed as instructed, and whether preliminary trends support decreases in anxiety and distress symptoms across the study duration.

Data Analysis

Quantitative data will first be analyzed descriptively; the recruitment, engagement, and attrition rates will be calculated, sample characteristics will be summarized (both across the total sample, and within each group) and mean scores on measures will be reported (within each group). Assessment of acceptability will be based on open-ended qualitative feedback regarding impressions of the VR intervention, which will be analyzed using content analysis with NVivo 12 software that was designed to assist with qualitative data organization. We will also determine acceptability based on the developed likert-scale questions. Means or medians will be reported depending on the distribution of the data. A triangulation approach will be used to amalgamate data sources and comprehensively assess acceptability. Paired samples t-tests and repeated measures analyses of variance will assess whether there are changes in participant-reported symptoms across the duration of the study within the active intervention group. If power permits, independent samples t-tests (or an analysis of variance, followed by post-hoc pairwise comparisons) will assess whether there are mean differences in PSA scores between: 1) the active and control intervention groups, and 2) the active intervention group and TAU (this will be examined descriptively if underpowered). We will also examine changes in physiological arousal (an objective indicator of distress), assessed via skin conductance and heart rate, between and within (i.e., during VR intervention vs. within OR) intervention groups, and will assess whether self-reported distress and anxiety scores are correlated with indices of physiological arousal. Physiological data will also be integrated in the VR technological paper (in development) to understand whether physiological indices change during the VR experience (indicative of immersion). Finally, if power permits, independent samples t-tests and analyses of variance will assess whether there are mean differences in patient-reported symptoms according to certain sample characteristics (e.g., age, clinically significant anxiety, history of previous surgery, type of surgery), both within the active intervention group and within the complete sample.

Phase 3 (underway)

Focus Groups

Ethical approval from the University of Manitoba Health Research Ethics Board was obtained to recruit participants from Phase 2 who indicated on their consent form they would be willing to serve as a patient partner/advisor for future development of the VR program. For those indicating “yes”, a research assistant followed up via telephone to assess continued interest in involvement. The focus groups are being led by the authors (RE, KR, GL, JB). The first focus group consisted of individuals randomized to the VR intervention (i.e., those who received the VR OR intervention prior to surgery) and took place virtually over Zoom. A second focus group was then conducted with individuals randomized to the TAU group or the VR control group (i.e., those who did not receive the VR intervention). This focus group occurred in-person at HSC and commenced with each participant trialing the VR OR prototype. Due to scheduling conflicts, an additional focus group for TAU participants is planned for December 2023, and an additional focus group with VR intervention participants is scheduled for January 2024. It is important to note, as we discuss below, the VR control group (i.e., Nature Treks) ended up being dropped due to slow recruitment, thus we only

ended up running the control focus groups with individuals randomised to TAU.

The focus groups commence by reviewing the purpose of the feasibility study and the VR prototype. A semi-structured question guide was developed by the research team including several open-ended questions regarding patients' experiences with the VR prototype, whether they believe it impacted their surgical experience, and recommendations for further development. After open-ended questions are asked, more specific questions regarding feedback on potential adaptation of the prototype are explored. The focus groups are audio recorded and transcribed using Trint software (Trint Ltd, London, UK). Qualitative data will be analysed using Reflexive Thematic analysis [75], [76], [77], examining themes identified by authors across participants.

VR Refinement

Based on the results of Phase 2 and the focus groups, additional modifications and changes are being made to the VR prototype. As part of the feasibility study, participants from Phase 2 were asked about any additional elements to be included in the VR simulation. Additionally, a co-investigator meeting was held in April 2023 where preliminary results from a case series proof-of-concept study (first 7 participants of the feasibility trial) were presented. Expert co-investigators provided additional input on modifications based on these initial case series findings. Collectively, based on the findings from the feasibility, expert input, and focus groups, a list of additional elements to be integrated into the VR will be developed (e.g., artificial intelligence integration, educational component, guided relaxation, exposure to the waiting room or recovery environments, etc.). People engaging with the VR OR will also be provided with the opportunity to customise their avatar to be more representative of themselves. This means participants will be able to change the avatar's skin colour and height to enhance embodiment. Efforts will also be undertaken to improve the diversity of the VR OR staff.

Based on results from the feasibility study, focus groups, along with expert input consensus, we will aim to begin the development of the final prototype in late 2023 to be completed by March 2024 for testing in a future randomized clinical trial.

Results

This study was funded by a New Frontiers in Research Fund (#322523 340300 2000), a nationally funded research grant supporting high risk and high reward transformative research, awarded to author RE as principal investigator in March 2019. Two extensions were provided on funding related to COVID-19 delays and parental leave of the principal investigator (RE). Author JS led a component of the feasibility trial for the purposes of her doctoral dissertation and given the novelty of this area, analyzed the first seven participants in a proof-of-concept case series format [78]. Phase 1 was completed in November 2021 and recruitment for Phase 2 commenced in December 2021, and will be completed in December 2023. Based on some of the initial challenges with recruitment, such as institutionally mandated shutdowns of clinical research, there were a few amendments to the initial protocol (Appendix 1). The two major changes to the protocol were initiated because of challenges with recruitment, which were related to the COVID-19 pandemic restrictions including university-wide research shutdowns, and changes to the formats of the Breast Health Centre's educational sessions (classes became virtual). We opted to exclude the VR control arm for the purposes of feasibility and proceeded with a 2-armed trial (i.e., VR intervention vs. TAU). We also expanded recruitment to all major oncological surgeries (instead of restricting to breast cancer surgeries) in November 2022. However, as of August 2023, there have been no non-breast cancer

surgery patients recruited. In June 2023, we received full ethical approval to conduct the focus groups and conducted the first two focus groups in August and September 2023, and the final focus group is scheduled for January 2024. Full feasibility results and results of the focus groups will be published following the completion of data collection and analysis. Following final development of the VR program, we will apply for additional funding to conduct an RCT of the final VR simulation in 2024.

Discussion

Despite the high prevalence of PSA and the significant health-related impact of PSA on perioperative outcomes, little research has examined feasible and accessible interventions. Empirically supported treatments for generalized anxiety, like cognitive behavioral therapy, are not obtainable prior to surgery for most patients in Canada, due to limited access to mental health professionals and limited time before surgery. To the best of our knowledge, there has not been any comprehensive immersive VR simulation to be implemented prior to surgery. An easily accessible simulation using VR has the potential to reduce PSA for a large number of Canadians, which may yield better postoperative health outcomes and cost-savings to the healthcare system as a whole. The final novel VR intervention we are developing is intended to be able to be used by patients independently (including in the comfort of their own homes) but also could be offered in hospital settings (including pre-anesthesia clinics) and be able to be easily customized for different surgical procedures under general anesthesia. The integration of VR in healthcare shows tremendous growth and promise [79]. Headsets are now commercially available at low cost, and advances in the technology create growing opportunities for easy implementation (e.g., standalone, wireless VR headsets). The release of the Apple Vision Pro in June 2023 is expected to further increase both awareness of VR, demand, and accessibility.

Limitations

The development of this research occurred during the peak of the COVID-19 pandemic and therefore there were unanticipated recruitment challenges and overall delays in development. Firstly, lockdown orders initially slowed the development and refinement of the VR OR prototype itself due to work from home orders. Once the prototype was completed there were further issues due to surgery delays, along with advisories against “unnecessary” hospital visits, and changes to how patients were initially approached for their interest in participating (Breast Health Centre changed from in-person to virtual education classes, and eventually some classes were cancelled altogether). Ultimately, from December 2021 to December 2022, only 8 participants were recruited. Of note, during this time, there were also intermittent periods where no clinical research could be conducted. However, from January to September 2023, an additional 15 participants have been recruited. This increase in recruitment may relate to changes in societal and healthcare practices (e.g., vaccinations, reduced COVID-19 hospitalizations, removal of public health mandates) and will be explored further in the feasibility analysis.

Although feasibility and pilot studies are critical in the development of new interventions, the generalizability of findings are limited. Therefore, when published, the results of the feasibility/pilot trial will need to be interpreted with caution. Relatedly, the focus of these three initial phases have been on oncological surgery patients, namely breast cancer surgery patients, which may differ in important ways from other non-cancer surgical samples. Additionally, within the VR program itself, there was one variation of the patient avatar, and it does not reflect differences in gender, body type, or ethnicity which may potentially decrease patient embodiment within the VR intervention and the

ecological validity on the day of surgery. Furthermore, we did not ask background questions related to ethnicity, sexual orientation, or disability, and therefore are limited in understanding feasibility aspects across diverse populations. The sample size is also underpowered to reliably detect effects but will be able to inform future RCTs in terms of design and implementation. Further, preliminary trends in the data will increase confidence in the potential utility of the intervention. Relatedly, the exclusion of the VR control group (i.e., non-OR VR) as per our amendment limits our ability to understand preliminary effects of the VR intervention. It is possible that any anxiety-reduction trends for the VR intervention group compared to TAU may relate to a factor other than the effect of the intervention itself (e.g., an additional appointment prior to surgery, the opportunity to discuss fears, etc.). It will be particularly important for future RCTs to include a comparable comparison group to elucidate potential mechanisms. A future RCT is planned to test out the final iteration of the VR OR, and we intend to compare it to a mobile phone-based intervention using the same components of the simulation as well as TAU. This will allow us to disentangle the potential additive effect of immersion that exists only in VR applications. Finally, recent research by our group [73] and others demonstrates that PSA for oncological surgery relates to a range of factors including uncertainty of health trajectory, recovery [80], [81], psychosocial implications of surgery, among others. Our prototype intervention only targets one component of PSA (i.e., exposure to the OR and information regarding induction), which may not result in meaningful reductions among those with PSA related to other factors. However, results from these three phases will allow us to refine the VR intervention to best meet the patients' needs and integrate all possible features to further ameliorate PSA (e.g., relaxation strategies). Future versions of the simulation may also include advanced VR features such as relevant haptic feedback as the technology develops further.

Conclusions

We are developing, testing, and refining a novel VR intervention aimed to reduce PSA prior to major oncological surgery using a general anesthetic. The development of the VR simulation is guided by both experts in the field and people with lived experience. VR is a promising tool given its ability to be broadly disseminated. This study will lay the groundwork for a promising intervention to reduce PSA prior to major oncological surgery, and future iterations could be easily adapted to other forms of surgery. This ultimately may have significant positive effects on patient health postoperative outcomes and patient experience along with cost-savings to healthcare systems in the future.

Authors' Contributions

The authors confirm contribution to the paper as follows:

Study conception and design: R El-Gabalawy, J Sommer, P Hebbard, K Reynolds, T Mutter, WAC Mutch, N Mota, JL Maples-Keller, R Arora, D Perrin, E Jacobsohn;

Prototype development: R El-Gabalawy, J Sommer, WAC Mutch, T Mutter, MSD Smith, C Proulx, VG Shaigetz;

Data collection: J Sommer, G Logan, J Benedictson;

Analysis: J Sommer, R El-Gabalawy, G Logan, J Benedictson, K Reynolds;

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All authors reviewed the results and approved the final version of the manuscript.

Acknowledgements

This research was funded by a Tri-Council New Frontiers in Research Fund (PI: El-Gabalawy). We would like to acknowledge the National Research Council of Canada, as well as Benjamin Meek, Marissa Bowsfield, and Eisi Mollanji, for assisting with research participants.

Conflicts of Interest

Dr. El-Gabalawy is the External Advisory Chair of the Center for Perioperative Mental Health at Washington University and receives an honorarium related to her service.

Abbreviations

APAIS: Amsterdam Preoperative Anxiety Information Scale
BRCS: Brief Resilient Coping Scale
HSC: Health Sciences Centre
NCCN: National Comprehensive Cancer Network
OR: Operating room
PC-PTSD-5: Primary Care PTSD Screen for DSM-5
PDI: Peritraumatic Distress Inventory
PITI: Preoperative Intrusive Thoughts Inventory
PROMIS: Patient Reported Outcomes Measurement Information System
PSA: Pre-operative state anxiety
RCT: Randomized controlled trial
SSRI: Selective serotonin reuptake inhibitors
TAU: Treatment as usual
VR: Virtual reality

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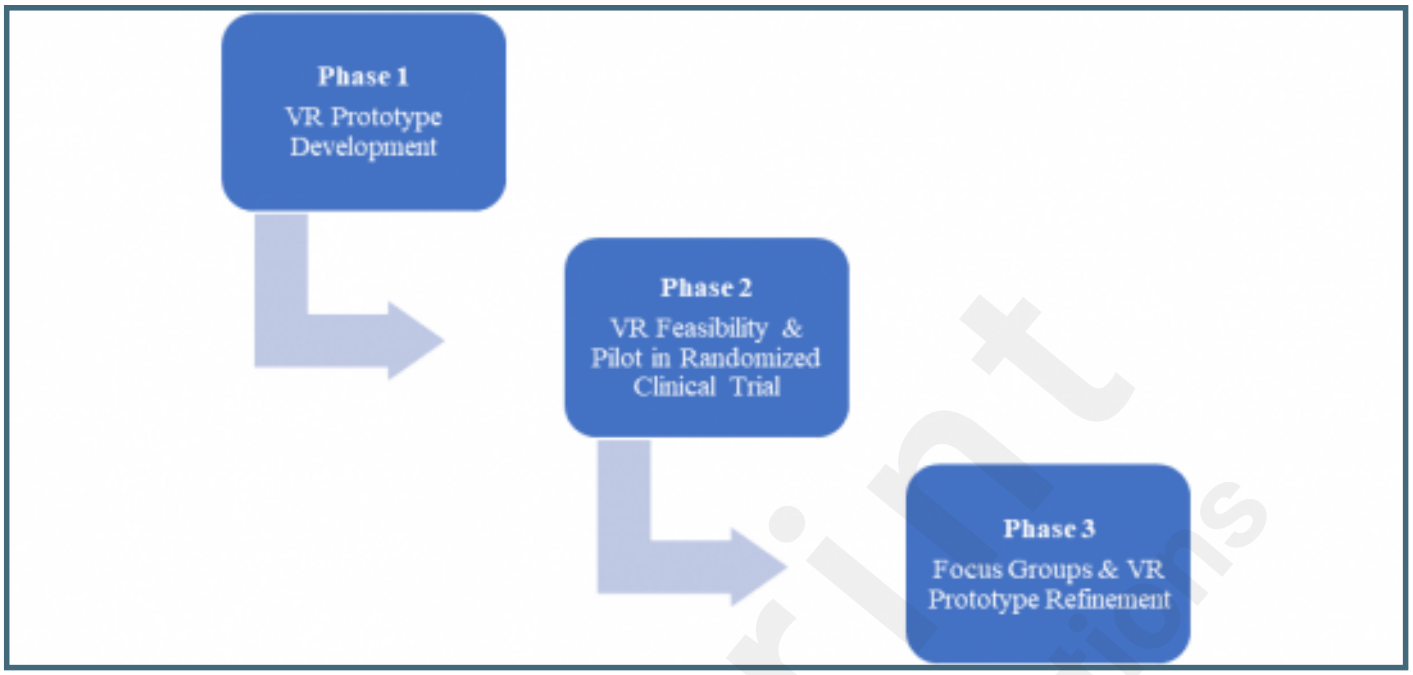
Supplementary Files

Figures

Flowchart of the three-phase development.



Screenshots of the immersive virtual reality operating room environment.

Virtual reality administration and set-up.

Multimedia Appendixes

Virtual reality study ethics amendment submission details.
URL: http://asset.jmir.pub/assets/542636b3c5e094162b42be9ae60e5fb2.docx

Funding Approval Letter and Feedback.
URL: http://asset.jmir.pub/assets/2374fe7aee44571c928af4dbb8b4cbb3.pdf

CONSORT (or other) checklists

CONSORT Checklist.
URL: http://asset.jmir.pub/assets/a933a10a11488b8c10ba6aa170021efa.pdf