Document Cover Page

Official Title of the Study:

Pilot Study for the Development and Implementation of a Virtual Reality-based Radiation Therapy Education and Anxiety Mitigation Program

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MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

Protocol Title: Pilot study for the development and implementation of a virtual reality-based radiation therapy education and anxiety mitigation program

MCW Protocol No.: PRO00032593
Patients will be enrolled at the following site(s): Community Memorial Hospital, St. Joseph's Hospital, Froedtert Hospital

Co-Principal Investigator: Carmen Bergom, MD, PhD Associate Professor Medical College of Wisconsin 9200 W. Wisconsin Avenue Department of Radiation Oncology Milwaukee, WI 53226 [redacted]	**Co-Principal Investigator** John LaDisa Jr., PhD Associate Prof. of Biomedical Engineering Marquette University & Medical College of Wisconsin 1637 West Wisconsin Avenue, room 311 Milwaukee, WI 53233 414-288-6739 John.LaDisa@marquette.edu
Co-Investigator: Sophia Shanahan, B.S. Graduate Student Biomedical Engineering Marquette University [redacted]	**Co-Investigator:** Melinda Stolley, PhD Health Psychologist Professor Medical College of Wisconsin 8701 Watertown Plank Rd. Milwaukee, WI 53226 [redacted]
Co-Investigator: Monica Shukla, MD Assistant Professor Associate Director, Radiation Oncology Residency Program Medical College of Wisconsin Department of Radiation Oncology 8701 Watertown Plank Rd. Milwaukee, WI 53226 [redacted]	**Biostatistician:** Anjishnu Banerjee, PhD Assistant Professor Division of Biostatistics Institute for Health and Society 8701 Watertown Plank Rd. Medical Education Building (MEB): M2460 Milwaukee, WI 53226 [redacted]

Sponsor/funding:
[redacted]

Study Schema

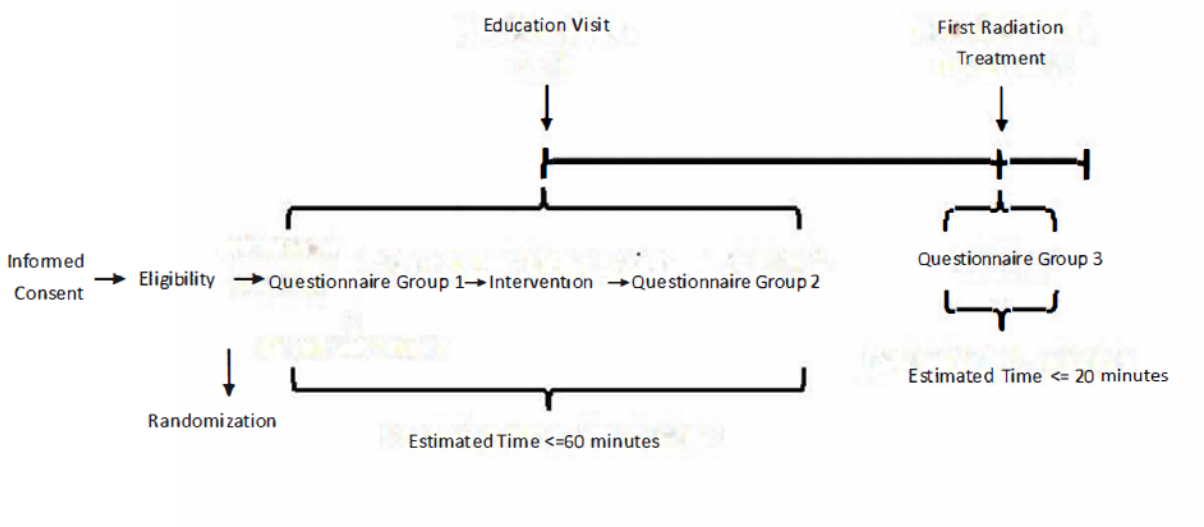

Figure 1: Study schema

1. **Questionnaire Group 1:**
   - STAI, INS, and "Questionnaire 1" (see Appendix 4)

2. **Questionnaire Group 2:**
   - STAI, INS, and "Questionnaire 2" (see Appendix 4)

3. **Questionnaire Group 3:**
   - STAI, INS and "Questionnaire 3" (see Appendix 4)

Study Calendar

Period/ Procedure Study Day/Visit Day	Screening Period in Preparation for Provider Visit	Breast Cancer Provider Visit	Education	First Radiation Treatment
Eligibility screening[1]	X			
Informed consent[2]		X		
Randomization[3]		X		
Questionnaire Group 1[4]			X	
Education Intervention[5]			X	
Questionnaire Group 2[6]			X	
Questionnaire Group 3[7]				X
Adverse Event Monitoring: Protocol Specific[AE; AN]			X	X

[1] If a patient meets initial eligibility criteria, they will be introduced to the study at a provider visit through a verbal description of the study.

[2] Patients will be provided an informed consent form at the breast cancer provider visit where they are first introduced to the study; if interested, patients can choose to sign the consent form at that visit, or take the consent form home and sign it at a future visit.

[3] Patients will be randomized to either the experimental (VR education) or control (standard education) with approximately 18 patients / group after being consented.

[4] Questionnaire Group 1 consists of the STAI, INS and "Questionnaire 1" and is provided before any education or RT.

[5] The education intervention consists of a VR education program for the experimental group and standard patient education for the control group (ASTRO video).

[6] Questionnaire Group 2 consists of the STAI, INS and "Questionnaire 2" and is provided immediately after the education intervention.

[7] Questionnaire Group 3 consists of the STAI, INS and "Questionnaire 3" and is provided immediately after the first fraction of treatment. Half of "Questionnaire 3" will only be completed by experimental group patients as it relates to improvements that could be made to the VR program.

[AE] ONLY complete AE form for AE's as described by the protocol. Add as an additional procedure to a visit.

[AN] As Needed

Table of Contents

List of Abbreviations

AE	adverse event
CRA	clinical research assistant
CRC	clinical research coordinator
CRF	case report form
CTO	clinical trials office
CTCAE	Common Terminology Criteria for Adverse Events
ET	exposure therapy
HMD	head-mounted display
ICF	informed consent form
INS	informational needs scale
IVET	in vivo exposure therapy
LINAC	linear accelerator
RCT	randomized controlled trial
RT	radiation therapy
SAE	serious adverse event
STAI	state-trait anxiety inventory
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
VAS	visual analogue scale
VR	virtual reality
VRET	virtual reality exposure therapy

1.0 BACKGROUND

Importance of the problem. 350,000 is the lower bound for the number of patients that receive radiation therapy (RT) for cancer treatment each year. Previous studies found that 60% of cancer patients endorse substantial anxiety in the preoperative stage of treatment and 80% of patients suffer from anxiety in the postoperative stage[1]. A standard of care for management of early stage breast cancer is a partial mastectomy, otherwise known as lumpectomy, followed by postoperative radiation therapy. The current study proposal is aimed at breast cancer patient education; 45% of breast cancer patients, specifically, suffer from anxiety[2]. The first conceptual framework for anxiety in surgical patients was provided by Janis et al in 1958, where preoperative anxiety was proposed as a predictive component of surgical outcome/success[1]. More recent studies published in medical and psychology journals have corroborated this finding by comparing the former with the latter in patients undergoing various types of surgery[3,4,5,6].

In 2012, Halkett et al published a study regarding the informational needs of breast cancer patients at different time points as they proceed through the radiotherapy treatment process. The study discusses the importance of addressing patients' informational needs through sensory and procedural information as a mechanism of anxiety reduction. The novel virtual reality (VR) approach proposed in this study aims to reduce anxiety levels and increase patient understanding by targeting what Halkett et al proposes as the cause of increased anxiety: a lack of treatment-related information[2]. Through an immersive audiovisual experience, the VR education module proposed in this study will sequentially guide the patient through the treatment procedure with accompanying sensory information (sights and sounds).

Critical barriers to mitigating the problem. Improved education about radiation-related treatments may help to reduce anxiety related to RT in cancer patients. Critical examination of the types of communication strategies used by the radiation team at the time of the radiation planning session did not demonstrate that communication differences could account for patient anxiety levels[7]. However, currently is it unknown whether immersive experiences that have the potential to better replicate treatment processes and educate patients about RT are feasible, can decrease anxiety, and/or can lead to improved patient satisfaction with their RT treatment experience.

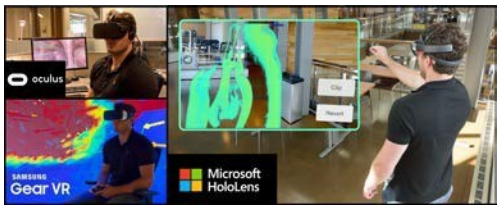

Figure 1. Examples of VR-based head-mounted displays including the Microsoft HoloLens, Oculus Rift and Samsung Gear VR. Each device permits 3D rendering and interaction in a virtual environment. The patient-specific content shown above was created in MARVL.

VR provides a computer-generated depiction of a real or an imagined environment[8]. For example, VR can be used to move through simulated buildings that do not yet exist, show blood flow through an artery in vivid 3D[9], or simulate health care procedures with no danger to a user. The use of VR-based audiovisual output devices allows human operators to experience the environment as if they were part of that world. VR worlds are ideally suited to training experiences, such as that proposed here. As mentioned above, immersion refers to the technical capability of the VR system to deliver a surrounding environment within which a patient can interact, and convincingly create a sense of presence within this virtual environment. This can be accomplished in an affordable and straightforward

manner with head-mounted displays (HMDs) that place a user into a virtual world through the use of an integrated optical system that is placed in front of the user's eyes (**Figure 1**). Another key feature of the VR experience is the ability to interact with the virtual environment in real-time. This interaction typically occurs through the use of external input devices ranging from a Bluetooth controller to preset actions that respond to the user's real physical motions exerted while exploring the VR world. Perhaps most importantly, the added value of VR for education is the possibility for the user to learn through first-person experience[8] and for that learning to be monitored and assessed through analytics from the user's interactions.

Building from exposure therapy. Studies show exposing an individual to a feared event or environment in a non-threatening setting can lead to positive treatment results[10]. Exposure therapy (**ET**) has served as the gold standard for many psychological conditions, including anxiety[11]. ET is usually conducted via *in vivo* mechanisms involving the physical world (e.g. patient with fear of elevators guided in riding one), but limitations include situational control, access to stimuli, financial and time constraints, and difficulty recreating a specific situation or fear[11]. More recent VR exposure therapy (**VRET**) avoids these limitations by creating the exposure though a realistic virtual reconstruction of a feared stimulus within a safe and controlled environment. VRET also allows for customizable and repeat sessions without additional cost or resources[11]. To test the clinical applicability of VRET, a recent study pulled 11 VRET randomized controlled trials (RCT) from major medical, health, and psychological literature and analyzed their effectiveness with various phobias and psychological disorders, including different types of anxiety. The study concluded VRET is an innovative application with serious potential towards treating psychological conditions[12]. Further, one meta-analysis published in the *Journal of Anxiety Disorders* compared VRET to in vivo exposure therapy (IVET) and control conditions in 13 cases and found VRET to be highly effective at treating various phobias and slightly but significantly more effective than IVET[13] while another meta-analysis comparing VRET with classical evidence-based interventions (i.e., cognitive-behavioral therapy with no VR exposure or behavioral therapy with no VR exposure) published in *Depression and Anxiety* found therapy involving VRET to be just as effective as classical evidence-based mechanisms[14]. While pre-treatment anxiety is not typically considered a clinical phobia, Andersen et al found 60-80% of patients receiving RT treatment to experience significant anxiety levels[1]. The effectiveness of VRET in post-traumatic stress, phobias, and anxiety disorders provides strong evidence for future success in treating anxiety in the current work.

Related Studies. The virtual environment for radiotherapy training (VERT) system was originally created as an RT training instrument for medical students studying to be radiation therapists. However, a recent study performed in Australia leveraged the impressive visual capabilities of the VERT system to present complex RT treatment concepts to 19 breast cancer patients as a form of preoperative education. The VERT education session consisted of an introduction to the VERT system in addition to educational information on the following RT treatment components: immobilization, simulation, and planning and treatment. Study measures included a demographic questionnaire and a 21-statement questionnaire that asked patients to rate their level of agreement regarding various features of the VERT system (i.e., structure, content, venue) on a 5-point Likert scale. Open-ended questions were also included to glean insight into aspects of the program that patients found most and least useful. The results of the second study measure showed high ratings towards the program content and delivery, with particular acknowledgement of the 3D visuals. The

authors found the results encouraging and supportive of the use of VERT in patient education. The conclusion of the study pressed for further utilization of the 3D visual capabilities of the VERT system in patient education to promote patient engagement and effectively transfer knowledge from clinicians to patients[15].

Another study measured patient anxiety and comprehension levels after providing preoperative patient education via the VERT system to twenty-two prostate cancer patients scheduled to undergo RT. The patients attended a classroom-based VR session, modeled as a linear accelerator flight simulator. The experience included complete immersion in a standard radiotherapy treatment room, a presentation of treatment-based objectives, and a digital anthropomorphic phantom for visualization of linear accelerator movement and laser beam positioning about the patient. Two questionnaires, one anxiety-focused and one comprehension-focused, were given to each patient both prior to and subsequent to the VR education program. Statistical analysis of the questionnaires found substantial results proving the authors' hypothesis that patient education in the form of a VR module decreases preoperative anxiety and increases treatment comprehension for patients[16].

A third study using VR patient education conducted an RCT in which 127 patients were assigned in a 1:1 ratio to either a standard or immersive preoperative education experience prior to a neurologic operation. The study objective was to make patients feel more comfortable in the treatment environment through information and VR preoperative treatment exposure. The VR demonstration consisted of a five-minute audiovisual VR video that presented the preoperative and postoperative experience through Oculus VR goggles. Patients were then given the opportunity to ask questions about the demo. This study used two scales: the Evaluation du Vecu de l' Anesthesie Generale (EVAN-G) score and the Amsterdam Preoperative Anxiety and Information (APAIS) score. The study concluded that patients subject to VR preoperative education had improved satisfaction following the surgical procedure[17].

2.0 OBJECTIVES

It is challenging to explain a complex topic such as radiotherapy to patients[15], but this education is critical as it has an impact on the quality of care provided from the patient's perspective[7]. Moreover, the quality of patient education is variable from practice to practice. Hence, there is a need to create and disseminate an interactive platform that improves the patient education experience and facilitates an increased level of patient understanding. The potential of VR is intriguing in this regard. VR uses rendered data, audiovisual cues, 3D viewing and motion response to replicate experiences from the physical world. Within the context of VR, the term *immersive* specifically refers to experiences that facilitate motion of a participant and a field-of-view that covers a user's gaze up to the level of peripheral vision (i.e., >180-degrees). Prior research on the use of VR for patient education demonstrates that a VR-based preoperative treatment exposure session can improve patient satisfaction ratings more definitively than prevalent pharmacologic and standard education anxiety-relieving interventions[17]. Unfortunately, there is a paucity of tools (content, software, specific protocols) and associated studies supporting the use of VR with breast cancer patients.

The *objective* of this pilot study is to create an immersive VR-based education program allowing breast cancer patients to experience the procedure and emotions associated with radiation therapy administered via a linear accelerator (**LINAC**) machine, before physical treatment occurs. The team assembled has the expertise to complete the proposed work, which was built from related information available in the literature. For example, studies suggest clinically relevant anxiety is associated with emotion-focused coping, difficulty communicating with the treating team, and a perceived lack of support from RT team members, but the subsequent inability of these factors to predict patient outcome underscores a need for additional tools such as those proposed in the current work. While a recent RCT using immersive VR for patients revealed improvements in preoperative patient anxiety, as well as perioperative patient experience and satisfaction, this work was performed in individuals undergoing elective neurosurgeries[17]. Based on this data, our *central hypothesis* is that **developing and incorporating VR content into the current RT patient education model will reduce anxiety levels and lead to better patient understanding of the treatment plan.** The central aim below will provide the foundation for a novel tool to reduce anxiety during an RT session, which represents a critical unmet need for patients facing RT treatment.

Central Aim. Assess patient anxiety and satisfaction after incorporating VR-based content into the current patient education model. Following consultation with the Clinical Trials Office, and consistent with current approaches for related patient research, the team has designed a protocol to assess patient anxiety, satisfaction and knowledge of the RT protocol. After noting any prior VR experience and education, groups of patients (approximately 18/group) will be exposed to VR-based content (Appendix 1) or a control audiovisual experience. A patient-reported outcome questionnaire consisting of the Informational Needs Scale (INS; Appendix 2), State-Trait Anxiety Inventory (STAI; Appendix 3), and Visual Analogue Scales (VAS; Appendix 4) for stress, preparedness, and satisfaction will serve as the primary study endpoints scrutinizing patient anxiety levels, treatment comprehension, and the VR content and experience. The second study endpoint involves improvements that could be made to the VR education program for future studies/use based on patient feedback. This post-interventional questionnaire will only be given to patients in the experimental group.

3.0 SUBJECT ELIGIBILITY

3.1 Inclusion criteria

(Y)_____Patient is 18 years of age or older
(Y)_____Patient is female
(Y)_____Patient has been diagnosed with breast cancer
(Y)_____Patient will be receiving whole breast radiation therapy without supraclavicular nodal irradiation
(Y)_____Patient is scheduled for an outpatient radiation oncology visit
(Y)_____Patient has the ability to understand a written informed consent document, and the willingness to sign it
(Y)_____Patient has the ability to complete a series of self-reported questionnaires

3.2 Exclusion criteria

(N)_____Non-English-speaking patients (as the VR education program includes English narration)
(N)_____Patients with visual defects that affect their ability to watch a movie
(N)_____Patients with auditory defects that affect their ability to listen with headphones
(N)_____Patients who have worked in the field of radiation oncology as they would have previously undergone treatment-related education
(N)_____Patients who have been treated previously with radiation oncology as they would have previously undergone treatment-related education
(N)_____Patients that have been diagnosed with epilepsy, conditions causing seizures, or have any previous history of seizures because a very minute number of head-mounted display (HMD) users have experienced a seizure as a result of using the device
(N)_____Patients with a reported history of cognitive disability as their ability to understand educational content may be impaired
(N)_____Patients with a history of severe motion sickness because a side effect of using a HMD in a very small number of users is motion sickness symptoms
(N)_____Patients with a pacemaker, hearing aid(s), and/or defibrillator, while patients with other types of electronic medical devices / implants will be assessed for eligibility on a case-by-case basis because there could be potential interference with the HMD

Physician's Signature _____ Date _____

Research Coordinator's Signature _____ Date _____

4.0 ACCRUAL GOAL AND STUDY DURATION

Data from approximately 36 patients is needed to meet study objectives. Patients will be randomized to an immersive VR intervention versus standard patient education session regarding the process of receiving radiation therapy. The approximate study duration will be 9 months to obtain data from approximately 36 patients. The study team has a high enrollment estimate of 60 patients to obtain data from approximately 36 patients.

5.0 SUBJECT REGISTRATION

After being introduced to the study and provided study details at a breast cancer provider appointment, interested patients will complete an informed consent form prior to enrollment in the trial. Patients will be consented by one of the radiation oncologists listed on the study team, Ms. Shanahan, a nurse or a clinical research assistant/clinical research coordinator(CRA/CRC) in the Clinical Trials Office of the Froedtert & Medical College of Wisconsin Cancer Center (please see eBridge form section 2 for study team members) depending on schedule availability.

All patients who are consented will be registered in OnCore®, the MCW Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements. Cancer stage and related diagnosis information for each patient will be collected from Epic.

Please call Carmen Bergom, MD, PhD, at [redacted] or Monica Shukla, MD at [redacted] if there are any questions regarding registration or eligibility.

6.0 STUDY DESIGN

The proposed study is a multi-site RCT. The study protocol will be conducted at three different RT treatment sites: Froedtert Hospital (Milwaukee, WI), Community Memorial Hospital (Menomonee Falls, WI), and St. Joseph's Hospital (West Bend, WI).

6.1 Education

6.1.1 Control Group Education

The control group will receive education in the form of an educational video created by the American Society for Radiation Oncology (ASTRO) (https://www.astro.org/Patient-Care-and- Research/Patient-Education/Patient-Videos). The ASTRO Radiation Therapy (RT) video provides audiovisual education for patients on RT. The ASTRO RT video is considered standard education at Community Memorial Hospital (CMH) and St. Joseph's Hospital. The video will be started for the patient by one of the radiation

oncologists listed on the study team, Ms. Shanahan, a nurse, or a CRA/CRC in the Clinical Trials Office of the Froedtert & Medical College of Wisconsin Cancer Center depending on schedule availability.

6.1.2 Experimental Group Education

The experimental group will receive education in the form of an immersive VR education program delivered via a HMD, similar in duration to the control group education. Patients will have the opportunity to be immersed in a CT simulation room, a dosimetry room, and an RT treatment room while a virtual model of a clinician delivers verbal educational content (please see the VR education script in Appendix 1). Patients will also have the opportunity to virtually undergo the RT treatment process through camera movements and animations that have been programmed into the VR program.

6.2 Baseline Visit

The baseline visit is the provider visit where eligible patients are introduced to/recruited for the study. Study objectives and the patient's potential role in the study will be discussed, and the patient will have plenty of time to pose questions to the research team. At this visit, interested subjects will be provided an informed consent form. No trial procedures will be conducted prior to a subject being consented.

6.3 Randomization

Approximately 36 patients (depending on withdraw rate) will be randomized into the control group and experimental group (approximately 18/group) via the randomization feature within the OnCore® system, and stratified by receipt of chemotherapy, if possible.

6.4 Intervention

A copy of the signed informed consent form (ICF) will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

Patients will be given Questionnaire Group 1; Questionnaire Group 1 consists of the STAI, INS and "Questionnaire 1" (see Appendix 4) and is provided before any education or RT.

The administration of the questionnaires will be conducted by one of the radiation oncologists listed on the study team, Ms. Shanahan, a nurse, or a CRA/CRC in the Clinical Trials Office of the Froedtert & Medical College of Wisconsin Cancer Center depending on schedule availability.

Subjects will then be briefed on the education intervention they are about to receive. Subjects in the control group will undergo a standard, non-immersive patient education experience. Subjects

in the experimental group will be taught how to use the VR HMD and undergo education in the immersive environment. The HMD instruction will be provided by either one of the radiation oncologists listed on the study team, Ms. Shanahan, a nurse, or a CRA/CRC in the Clinical Trials Office of the Froedtert & Medical College of Wisconsin Cancer Center, depending on schedule availability.

At the end of the education intervention, patients will complete Questionnaire Group 2; Questionnaire Group 2 consists of the STAI, INS and "Questionnaire 2" (see Appendix 4) and is provided immediately after the education intervention. The completion of the two groups of questionnaires, with the education intervention is expected to take less than 60 minutes in total. Patients will have time to ask questions regarding the education and/or any concerns they may have to their treatment team.

After the first fraction of RT, patients will be given Questionnaire Group 3; Questionnaire Group 3 consists of the STAI, INS and "Questionnaire 3" (see Appendix 4) and is provided immediately after the first fraction of treatment. The second page of "Questionnaire 3" in this group is used to improve the VR content and its delivery via input from patients, and therefore is only completed by members of the experimental group. Iterative adjustments to the VR program will be implemented after completion of the current proposed study based on rankings of importance and frequency. In this manner, future studies using VRET with radiation oncology will benefit from the use of this human-centered design approach.

Patients may withdraw from this study at any time, and experimental group patients will be instructed that they should remove the VR HMD if they feel any discomfort while wearing it. If a patient withdraws from the study, no further information will be collected on that patient and another eligible and interested patient will be consented to meet the study accrual goal, as budget permits.

There will be no long-term follow-up for subjects in this study.

Table 1: Estimated completion times for individual questionnaires, the education intervention, and questionnaire groups

Activity	Time (min)	Questionnaire Group Total (min)
STAI	10	
INS	10	
Questionnaire 1	2	**Group 1:** 22
Education Intervention	20	
STAI	8	
INS	8	
Questionnaire 2	2	**Group 2**: 18
STAI	8	
INS	8	
Questionnaire 3	2	**Group 3**: 18

7.0 SUBJECT WITHDRAWAL CRITERIA

In the absence of treatment delays, educational study may be completed unless:

- Disease progression
- General or specific changes in the patient's condition render the patient unacceptable for further questions in the investigator's judgement
- Inter-current illness that prevents further involvement in the study
- Patient decides to withdraw from the study
- Significant patient non-compliance with protocol
- Unacceptable adverse event(s)

Patient-Initiated Withdrawal: A patient may decide to withdraw from the study at any time and experimental group patients will be instructed that they should remove their VR HMD if they feel any discomfort while wearing it.

Investigator-Initiated Withdrawal: The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's noncompliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Subjects may call Dr. Carmen Bergom at [redacted] or the study's Clinical Research Coordinator/nurse to be withdrawn from the study. No further data will be collected from a subject who has withdrawn from the study. Information collected prior to subject withdraw is required to be kept. As budget permits, the next RT patient that meets the eligibility criteria and expresses interest in the study will be enrolled to meet the study accrual goal.

8.0 ADVERSE EVENT REPORTING

Table 2: Description of adverse events that will be reported in this study

Adverse Event	Study Arm Affected	Reportable Timeframe
Key linking subjects to their alpha-numeric identifier is subject to unauthorized access or lost	Control and Experimental	At any point throughout the duration of this study
Blackout / loss of awareness[18]	Experimental	While the subject is undergoing VR education
Seizure[18]	Experimental	Within 12 hours of using the head-mounted display (HMD)
- Nausea[18] - Disorientation[18] - Dizziness[18] - Eye strain[18] - Impaired balance[18] - Visual abnormalities[18] (i.e. blurred or double vision) - Discomfort or pain in the head or eyes[18]	Experimental	Reported if symptom is described by patient as being severe, mild cases do not resolve within 30 minutes of removing the HMD, or symptom presents post-use within 12 hours of using the HMD
Onset of a contagious condition that could have spread through transfer of the HMD[18] such as pink eye or a cold	Experimental	Within 48 hours of using the HMD
Skin irritation[18] that could have resulted from wearing the HMD or using the hand controller	Experimental	Within 12 hours of using the HMD

This team will follow the Medical College of Wisconsin policies related to adverse event reporting. This information may be found on the Human Research Protection Program website.

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others (UPIRSO). This information may be found

on the Human Research Protection Program website.

9.0 STATISTICS

A prior study[17] reported effect sizes of approximately 0.97 standard deviations (the standard deviation estimated from the reported confidence interval) when using a VR based intervention for anxiety scores (abbreviated as APAIS scores in the referenced study). Using these numbers, with about 18 patients in control and test (i.e., VR experience) groups, we will be able to detect statistically significant effect sizes of 0.97 or larger for differences in means in pre-post changes of measures between the groups, with at least 80% power, at the 0.05 type I error level, with two sided tests. Block sizes of 6 will be used for the randomization. These are estimates for our pilot study, meant to guide sample size and statistical design for larger studies. Calculations are based on Cohen's method using the "pwr" package in R software.

The study team estimates an enrollment number of 60 patients will guarantee that data is obtained from approximately 36 patients. This is a high estimate to be on the safe side when creating the OnCore® build.

Descriptive and exploratory analysis will include one-sample paired t-test(difference pre vs post), Cohen's d, Wilcoxon signed-ranked test, sensitivity analysis, in addition to tabulations of the number of patients, mean score, standard deviation vs confidence intervals, age, race, and other related covariates including education, occupation, receipt of chemotherapy, diagnosis/cancer stage, previous VR experience, and sources of support.

The principal hypothesis of interest is whether measure score changes between different time points vary between the test and control groups. To measure the difference in measures in patients, we will use a mixed multivariate regression model. This model will account for multiple measurements from the same patient (e.g., measurements of VAS scores at 3 time points) through a random effects term accounting for individual patient variations. Multiplicity corrections wherever needed will be done using the Holm-Sidak method. All statistical analysis will be conducted on SAS and/or R software.

The STAI will be analyzed as an individual questionnaire as the patient-reported values for each measure are summed for an overall questionnaire score, while each item on the other questionnaires will be analyzed individually as we are looking to see if changes exist for each patient between the three different data collection time points. The questionnaire results will be reported in aggregate.

All patients will be instructed to fill out each item on each questionnaire. Regression models named above can typically accommodate missing data (for example, responses for all time points from a patient are not recorded), imputation will therefore not be considered. Missingness will be investigated to explore evidence for informative missingness, if any; appropriate adjustments such as inverse probability weighting will be used to adjust for any informative missingness.

10.0 DATA MANAGEMENT

Study questionnaires will be completed by the patient in hard-copy format and entered into OnCore® via standardized case report forms (CRFs), in accordance with the study calendar, using single data entry with a secure access account. If desired for analysis purposes, data may also be entered into a password-protected Excel sheet. Data will be entered by a member of the study team or a member of the Clinical Trials Office (CTO). The original hard copies of data will be locked within a secure-access building and a secure access office and/or cabinet. Data that is transported between sites involved in this multi-site study (i.e., from CMH to Marquette University) will be transported on an encrypted flash key and then stored on a private, network-attached share drive.

Further, upon enrollment in the study, all patients will be assigned a unique alpha-numeric code to be used as identification on all hard-copy study questionnaires in place of their name, thereby minimizing the risk associated with the unlikely but potential risk of unauthorized questionnaire access. The key linking patient's name to unique identifier will be locked within a secure-access building or on a password-protected file/system.

All source documentation and data will be available for review/monitoring by regulatory agencies.

11.0 Risks and Benefits

11.1 Risks

Table 3: Includes risks and mitigation tactics associated with this low-risk study

Risk	Risk Mitigation
HMD could have side effects including but not limited to motion sickness, nausea, disorientation, and dizziness[18] (please see 8.0: Adverse Events Table for more information)	Slow camera movements and fade-in/fade out between scenes were a part of the VR education module design to minimize triggering of any of these symptoms. Patients will be informed that they should remove the HMD if they feel any discomfort.
The goal of this study is to provide a novel source of patient education by developing an immersive VR program that realistically replicates the treatment experience and enables patients to feel a strong sense of presence in the virtual treatment room. A potential risk associated with this goal is if patients are incredibly anxious about the radiotherapy treatment process, the VR experience may also induce anxiety.	Patients will be informed that they should remove the HMD if they feel any discomfort. Patients should talk to their radiation oncologist if they feel anxiety regarding their treatment.
Contagious conditions, such as those in the eyes, nose, or scalp, may transfer between different users of the device[18].	Patients with a known infection/contagious condition will not undergo the VR experience if they are considered to be contagious. Further, the HMD will be cleaned between each use with germicidal wipes (i.e. Purell).
Patient responses to surveys could potentially be leaked/ subject to unauthorized access and be used in a way that could embarrass the subject. Further, someone could find out a patient is in this study.	Hard-copies of patient-completed questionnaires will remain locked inside of a cabinet in a secure-access building. Responses from these hard-copies will also be entered into OnCore® and potentially stored in a password- protected format on private, network-attached shared drive. Transportation of data, if necessary, will occur on an encrypted flash key. Further, upon enrollment in the study, patients will be assigned a unique alphanumeric identifier, so their name will not be attached to hard-copies of the study questionnaires. The study will be discussed with the patient in a private setting.

The VR HMD blocks view of the outside world. Patients could potentially bump into something or fall because they cannot see what is around them at the time of use.	Patients will sit down while experiencing the VR education program. Pre-determined movement about the virtual treatment room has been implemented by moving the camera in the scene, so patients will not need to conduct any physical navigation

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

11.4 Benefits

Table 4: Benefits of Study

Potential Direct Benefit to Subject	**Benefit to Science**
The goal of the current study is to lessen the burden that pre-treatment anxiety unfortunately places on many breast cancer patients' lives. Through familiarizing patients with the sights and sounds of radiotherapy by presenting a VR program designed to give patients a strong sense of presence in a virtual treatment room, and increasing comprehension with educational narration and interactive mechanisms designed to promote patient-engagement, we believe that patients in the experimental group may be less anxious about their treatment in the time period leading up to the first fraction of treatment, and during treatment.	If the hypothesis of this study is met (i.e., VR patient education is shown to provide increased comprehension of upcoming treatment procedures and decreased anxiety levels), then VR education programs may be become more widespread and used in accompaniment to standard education interventions when those interventions alone are not enough to explain to patients the complex nature of a given treatment. We are also not limited to breast cancer treatment, but if this study proves successful (as the limited number of related studies have) then over time, a multitude of treatments may have their own accompanying VR patient education programs, thereby decreasing anxiety and increasing comprehension for all types of patients at a national, and potentially global level.

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Appendix 1: VR Education Script - Excluded for Copyright reasons

Appendix 2: INS - Excluded for Copyright reasons

Appendix 3: STAI - Excluded for Copyright reasons

Appendix 4: Questionnaires - Excluded for Copyright reasons