Virtual Reality Biofeedback for Postpartum Anxiety and Depression (VITALISE)

Protocol Number: **STUDY21040063**

Version Date: 09/05/2023

Version Number: 2

NCT registration NCT04925765

Principal Investigator: Dr. Grace Lim, MD, MSc

Source of Funding: Internal University of Pittsburgh

History of Protocol Versions:

Version	Date	Sections Changed	Rationale for the Change
1.0	September 1, 2021	N/A	IRB approval 06/03/2021
2.0	September 5, 2023	Updated for clarity	ClinicalTrials.gov update

Contents

ABBREIVATIONS AND ACRONYMS

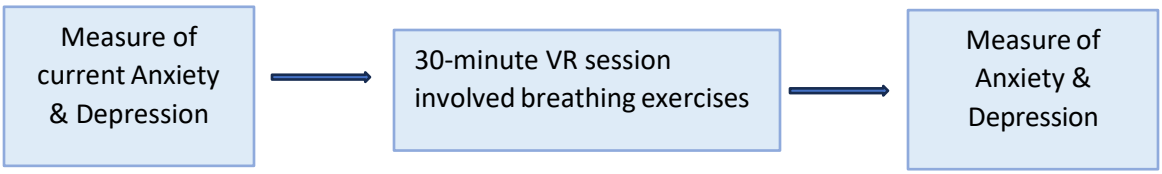
AE	Adverse Event
ANX	Anxiety
CFR	Code of Federal Regulations
CRF	Case Report Form
DEP	Depression
EPDS	Edinburgh Postnatal Depression Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HMD	Head mounted display
IRB	Institutional Review Board
NCT	National Clinical Trial
PI	Principal Investigator
SAE	Serious Adverse Event
STAI	State-Trait Anxiety Inventory
UPMC	University of Pittsburgh Medical Center
VR	Virtual Reality

1 Protocol Overview

Study Description	This project investigated whether a VR breathing intervention would reduce depression and anxiety symptoms in postpartum women with a history of depression and anxiety.
Study Population:	Six postpartum women with a history of anxiety or depression. All women were proficient in English reading and speaking.
Planned Sample Size:	10 women were anticipated to participate; 6 completed the study protocol
Participating Institutions (if a multi-center clinical trial)	University of Pittsburgh, UPMC Magee Women's Hospital

1.1 Study Schema

Figure 1. Timeline of all Study Procedures.



2 Background and Rationale

2.1 Background

Cognitive behavioral therapy is a basic element of treatment for postpartum anxiety (ANX) and depression (DEP)[1]. Exacerbations of existing DEP and ANX are rising in concert with the COVID-19 pandemic[2], with limited supply of mental health professionals that are trained to help these patients. Virtual Reality (VR) offers a potential solution to these care gaps, and VR has demonstrated success in treatment of pain, chronic disease, and other mental health conditions[3-4]. However, VR effectiveness for treatment of postpartum ANX or DEP has not been investigated. The purpose of this pilot trial is to test patient feasibility and acceptability of virtual reality biofeedback program in pregnant and postpartum women for ANX and DEP outcomes.

2.2 Rationale

This study will assess the feasibility and acceptability of a headset-based virtual reality protocol to reduce anxiety and depression within women who have a history of anxiety or depression.

3 Hypotheses, Objectives and Endpoints

3.1 Hypotheses

3.1.1 Primary Hypothesis

We hypothesized that the headset-based virtual reality system would be feasible as a management tool for the treatment of anxiety and depression and that women would find this method of treatment acceptable to use.

3.1.2 Primary Aim:

To determine the feasibility and acceptability of the use of a virtual reality breathing simulation for the treatment of anxiety and depression

3.1.3 Secondary Aim:

To identify changes in depression and anxiety from baseline to post treatment.

4 Research Design: Prospective Observational

Overview of Visits/Encounters with Participants:

This is an open label, prospective pilot clinical trial. The individual patient's active participation is approximately two hours.

5 Human Subjects

5.1 Subject Population

Six postpartum women with a history of anxiety or depression participated in a single VR biofeedback session.

5.2 Inclusion Criteria

- Recently postpartum (delivery within 3 months) women
- Diagnosed history of anxiety or depression

5.3 Exclusion Criteria

- Unable to participate in study procedures.
- English illiterate

5.4 Recruitment Methods

In conjunction with clinical teams in the outpatient clinics, Dr. Lim and the study team will identify patients eligible for the study, introduce the research to them, and obtain permission for the study team to approach them about potential participation. Dr. Lim has direct access to potential participants as a clinical at UPMC Magee Women's Hospital; as a consultant anesthesiologist Dr. Lim also has direct access to the same patients as a clinical caregiver and service administrative leader as the chief of obstetric anesthesia. Dr. Lim and the study team will work directly with clinical directors from each community practice to both identify and introduce the study to potential participants.

In addition to that, University of Pittsburgh Pitt+Me Registry will be used as a recruiting tool. Once a participant has contacted Pitt+Me with an interest in the study, a Pitt+Me recruitment staff will call them for a brief pre-screen. If they pass the pre-screen and agree to be further contacted for additional screening, a study coordinator will directly reach out to the interested individual for a phone screening.

6 Research Activities

Summary of Experimental Procedures:

Utilizing head mounted display (HMD), smartphone with software rendering stereoscopic images to the user and heart rate/respiratory rate sensors connected and displayed. There is a 30-minute VR session involved breathing exercises: users saw objects in a virtual world which changed movements with their breathing. Measuring pre and post session anxiety and depression symptoms were measured by Edinburgh postnatal depression scales (EPDS) and State-trait anxiety inventory. Acceptability was assessed by questions, “Would you participate in another session?” and “would you participate in regular repeating sessions?”.

6.1 Screening Procedures

The screening procedures pertain to specifically women with a history of anxiety and depression. Medical record review will be completed to identify eligible participants for this study. Medical record review is a minimal risk activity that presents no additional risk beyond standard of care procedures. Any information obtained from these medical record reviews on subjects deemed ineligible will be immediately destroyed.

In conjunction with Dr. Lim, for patients recruited during the postpartum period, the study team will identify patients eligible for the study, introduce the research to them, and obtain permission for the study team to approach them about potential participation. As stated above, as a consultant anesthesiologist Dr. Lim also has direct access to the same patients as a clinical caregiver and service administrative leader as the chief of obstetric anesthesia. Patients will be identified through existing recruitment channels from the community OBGYN clinics and through prospective review of the OR C-section schedule.

The clinical team will notify the patients of their eligibility for the study; potential participants who express interest in learning more about the study will be referred to the study coordinator team. The study team will approach and enroll them into this research. The patient will be approached by the study team to fully explain the study, answer any questions the patient might have, and obtain informed consent postpartum.

6.2 Research Procedures

Baseline Assessment:
Once informed consent is obtained subjects will complete baseline measurements which include a demographics form, State-Trait Anxiety Inventory (STAI), and Edinburgh Postnatal Depression Scale (EPDS). An intrapartum form will also be completed via medical chart review.

VR Assessment:
The VR intervention consists of three key hardware components required for use. 1) a plastic Virtual Reality Headset (also known as HMD: Head Mounted Display), which covers a user’s eyes and is secured to their head using elastic straps which can be tightened with Velcro. The HMD houses a 2) smartphone which runs the Flowly software and renders stereoscopic images which are presented to the user through the HMD. The phone connects to 3) a Bluetooth heart rate monitor which gathers heart rate data and clips simultaneously to the user’s ear lobe using a spring-loaded clip and to their clothing.

The subject will download an app to their smartphone that will transmit data to Amazon Web Services managed by Tamade, LLC. Subjects will be lent an iPhone if they do not have an iPhone or version that can support the VR sessions. In the case that subjects do have an iPhone 6s/6s+ or higher (iPhone 6/6+ not eligible), they will be asked to use it for the completion of the study.

Subjects will be given the mobile system VR Shinecon head mounted display (HMD) and Bluetooth sensors to provide patients Virtual Reality biofeedback sessions targeted for depression/anxiety. While the participant is using the VR intervention, the following outcome measure will be gathered: pain level, heart rate, and respiration will be taken via the device and smartphone app and stored in a database hosted by Amazon Web Services and managed by Tamade, LLC.

Subjects will then complete in a 1-hour VR session. In terms of the experience of the VANISH intervention, most exercises focus on breathing. Users will see objects in a 3D virtual world which change movements with their breathing and the user will be guided to use these in manners that manage body responses. Breathing resonance variation will be collected from the subjects during these exercises using the VR device. Training on how to complete these breathing exercises will be initiated as a part of the device-training.

Follow-up Assessment:
To conclude, a post-assessment STAI and EPDS will be repeated, as well as post-assessment feasibility questionnaire.

The subjects will participate in a total of 2-hours to complete all questionnaires and the VR session.

7 Potential Risks and Benefits

7.1 Reasonably Foreseeable Risks Related to Research

Risk associated with collecting and storing PHI. Both common and infrequent risks include a loss of confidentiality.

Risk associated with use of virtual reality devices. No common risks are noted. Infrequent risks include the potential for patient to feel frustration, anxiety, or uncomfortable due to the device visualizations.

7.2 Potential Benefits

There is no direct benefit.

8 Protection Against Risks

8.1 Management of research related risks

Risks are associated with screening procedures and risks associated with Breach of Confidentiality in the collection and storage of PHI:

There is a risk of "breach of confidentiality" of the screening procedures. To protect against this risk, all screening procedures will be done by study staff who have been completely trained in HIPPA/privacy procedures; all information will be kept in a locked and secure location; all data associated with the study screening will be stored against a random study ID number; any linkages between study ID number and patient identification will be separated, password

protected and stored behind UPMC firewall. To protect against the possibility of breach of confidentiality, all data collected will be identifiable only by a unique subject ID number, and no personal identifiers will be stored with data. Linkage files identifying subjects will be stored only in physical records that are kept in locked files accessible only by study staff; electronic data will be handled and protected as described above. Only consent forms will have identifiable information, and those will be kept in their chart separate from any data. Data will be labeled only with participant ID number. We will also conduct research interviews in a private room. We will collect only sensitive information limited to the minimum necessary to achieve the aims of our research. No sensitivity information will be shared via text-messages or emails.

9 Adverse Events and Serious Adverse Events

The proposed observational study will use the FDA definition of SAE. A serious adverse event is any untoward event that is thought by either the investigator to be unexpected and at least possibly related to the study and results in any of the following:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of an existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly or birth defect
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

9.1 Severity

The severity of adverse changes in physical signs or symptoms will be classified as follows:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.
- Grade 2 (Moderate): minimal, local or noninvasive intervention indicated.
- Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care/ADL.
- Grade 4 (Life-threatening): consequences; urgent intervention indicated.
- Grade 5 (Death): event is a direct cause of death.

9.2 Relatedness

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The event cannot be explained by concurrent disease or other drugs or chemicals.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The event occurs within a reasonable time after administration of the study protocol, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study protocol). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- Unlikely to be related – An event whose temporal relationship to study protocol administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study protocol) and in which drugs, chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study protocol administration, and/or evidence exists that the event is related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.3 Expectedness

The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described.

9.4 Reporting Serious Adverse Events

Any SAE, which is determined by the PI to be unexpected and at least possibly related to study, will be reported to the IRB as soon as possible. The PI report to the IRB will include all known details regarding the nature of the SAE.

Life-threatening or fatal unexpected adverse events associated with the study procedures must be reported to the IRB within 24 hours of discovery of the incident with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB. Outcomes of SAEs will be regularly reported to the IRB. A summary of the SAEs that occurred during the previous year will be included in the annual progress report as well as in the annual IRB renewal.

9.4.1 Adverse Events Reporting Timeline

Life-threatening or fatal unexpected adverse events associated with the study must be reported to the IRB within 24 hours of discovery of the incident with subsequent follow-up submission of a detailed written report. The IRB will be notified by telephone or facsimile transmission of a human adverse event that is fatal or life-threatening no later than 7 calendar days after receiving the respective human adverse event information, followed by the subsequent submission of a written Safety Report. Serious and unexpected adverse events associated with the study protocol will be reported to the IRB with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB.

9.4.2 Ensuring necessary medical/professional intervention for adverse events.

If there is a suggestion that any research procedures have resulted in an injury to subjects, there will be immediate contact with the Principal Investigator who is listed on the first page of the informed consent documents. Emergency medical treatment for injuries solely and directly related to participation in this research study will be provided by the hospitals of UPMC. Insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to patients/subjects. If research-related injury requires medical care beyond this emergency treatment, subjects will be responsible for the costs of this follow-up care. Currently, there is no plan for any additional financial compensation for these events.

10 Withdrawal of Subjects and Stopping Rules

10.1 Adverse Events Requiring Discontinuation

For this study, a serious adverse event is any untoward clinical event that is thought by either the investigator or the sponsor to be related to the study and results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of an existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly or birth defect
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

If clinically important and unexpected adverse experiences or clinically important study-related adverse experiences occur, they will be recorded on the adverse event case report form.

10.2 Other Criteria Requiring Discontinuation

Withdrawal of Subjects for reasons other than Non-compliance or Adverse Events:

- Protocol non-adherence: non-adherence at follow-up visits at the judgement of the PI
- Incomplete survey data, defined as missing 20% or more responses

11 Statistical Analysis

11.1 General Approach

Baseline demographic characteristics will be collected and analyzed using descriptive statistics.

Feasibility of the study is measured as the number of patients who report that the study was both 1.) easy to use and 2.) The session was worth my time.

Acceptability was measured as “yes” responses to both questions, “would you participate in another session in the future? 2. Based on your experience today, would you participate in regular repeating sessions (e.g., daily, or weekly)?”

Anxiety and depression are measured as continuous variables at baseline and after VR intervention. Due to the small sample size, only the number (proportion) of patients whose overall anxiety and depression scores changed/decreased from baseline to post-intervention will be reported.

11.2 Sample Size Determination

This is a sample of convenience as a pilot trial. We believe five complete subjects' answers will give us adequate information about feasibility and some estimations on measured outcomes to perform a sample size calculation for the fully powered trial.

11.3 Analysis of Primary Endpoint

To explore the feasibility of use of Virtual Reality as a method to aid in the reduction of anxiety and depression in postpartum women.

11.4 Analysis of Secondary Endpoint

To further explore change in anxiety and depression across the trials.

12 Data and Safety Monitoring

Dr. Lim will be responsible for data and safety monitoring. She will meet bi-weekly with study personnel to review the progress of the research study, including subject recruitment and retention and an assessment of the timeliness and quality of the data. Dr. Lim will review all data, procedures, and any adverse events that occurred. All adverse events, including breach of confidentiality, will be reported to the IRB at minimum at the time of renewal per their policies and procedures.

13 Regulatory, Ethical, and Study Oversight

13.1 IRB Approval

The PI obtained IRB approval **STUDY21040063**, from the University of Pittsburgh IRB, for the approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The IRB will review and approve the Informed Consent Document for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or obtaining consent from any participants. Moreover, the study will be reviewed at a minimum of annual basis (or more frequently as deemed necessary) by the IRB committee. Each participant will sign the approved Informed Consent Form prior to participating in the study.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable ICH Guidelines on GCP.

13.2 Informed Consent Procedures

Details of Participant Recruitment:

Medical record review will be completed to identify eligible participants for this study. Medical record review is a minimal risk activity that presents no additional risk beyond standard of care procedures. Any information obtained from these medical record reviews on subjects deemed ineligible will be immediately destroyed.

In conjunction with Dr. Lim, for patients recruited during the postpartum period, the study team will identify patients eligible for the study, introduce the research to them, and obtain permission for the study team to approach them about potential participation. As stated above, as a consultant anesthesiologist Dr. Lim also has direct access to the same patients as a clinical caregiver and service administrative leader as the chief of obstetric anesthesia. Patients will be identified through existing recruitment channels from the community OBGYN clinics and through prospective review of the OR schedule.

The clinical team will notify the patients of their eligibility for the study; potential participants who

express interest in learning more about the study will be referred to the study coordinator team. The study team will approach and enroll them into this research. The patient will be approached by the study team to fully explain the study, answer any questions the patient might have, and obtain informed consent postpartum.

In addition to that, University of Pittsburgh Pitt+Me Registry will be used as a recruiting tool. Once a participant has contacted Pitt+Me with an interest in the study, a Pitt+Me recruitment staff will call them for a brief pre-screen. If they pass the pre-screen and agree to be further contacted for additional screening, a study coordinator will directly reach out to the interested individual for a phone screening.

Individuals will be provided with full explanation of study-related goals and procedures. Questions will be answered for the patient as well as their support people. Patients will be given as much time as they desire to read the consent form and materials and ask questions. If desired, patients can take materials home for review and will be consented to participate via videoconferencing software and electronic consent via REDCap.

13.3 Protocol Deviations

Clinical research investigators and staff will be familiarized with the study protocol, GCPs, and applicable federal regulations to ensure that the study protocol procedures are followed. When a deviation is perceived to have occurred, the procedure completed will be verified against the study protocol, applicable regulations and relevant GCP principles. Deviations in the study protocol will be identified verbally and in writing to the PI and/or study coordinator as they occur. In addition to deviations noticed during completion of study protocol procedures, deviations may be identified through routine monitoring visits or audits of the clinical research records, as the research team will meet weekly to review the study recruitment, procedures, and retention. All deviations will be verified and presented to the PI for timely assessment and IRB reporting, if warranted. Any deviation, regardless of severity, will be recorded in the Non-compliance/deviation log by the PI or research staff member as they occur. Protocol deviations that do not meet the definition of IRB reporting requirements will be subject to yearly review and evaluation during the continuing review period.

Reportable incidence of Non-compliance includes any protocol deviation that:

- Significantly adversely affects the safety, rights, or welfare of the research participants, OR
- Significantly compromises the quality or integrity of the research data (i.e., negatively impacts the ability to draw conclusions from the study data), OR
- Represents Continuing Non-compliance (i.e., has been previously reported or represents a pattern of ongoing non-compliance).

I**ncidents of Non-compliance that do not meet the IRB reporting requirements** will be documented in a Non-compliance/deviation log and managed as part of the Data and Safety Monitoring Plan. The Non-compliance/deviation log will be kept throughout the study and the documentation will be made available upon request.

14 References

1. PMID: 29914574
2. PMID: 33964789

3. PMID: 34036696
4. PMID: 33952318