Study Title: Feasibility and Acceptability of ReCognitionVR-Based Cognitive Stimulation in Surgical Patients

PI: Dr. Hina Faisal

Department of Surgery

Houston Methodist Hospital

NCT Number: NCT06232317

Protocol Date: August 8, 2023

PROTOCOL TITLE:

Feasibility and acceptability of ReCognitionVR-based cognitive stimulation in surgical patients.

PRINCIPAL INVESTIGATOR

Hina Faisal, MD
Houston Methodist Hospital/Department of Surgery

CO-INVESTIGATORS/ COLLABORATORS:

Jiaqiong Susan Xu, PhD
Houston Methodist Hospital TMC/ Biostatistics in Medicine

Faisal Masud, MD, FCCP, FCCM
Houston Methodist Hospital TMC/ Clinical Anesthesiology & Critical Care

SPONSOR / FUNDING AGENCY

Houston Methodist Hospital

National Institute of Health (NIH)/National Institute on Aging

VERSION NUMBER/DATE

v.1: 08 August 2023

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change (Yes/No)

1. Study Summary

Virtual reality (VR) imitates reality by creating an artificial three-dimensional (3-D) environment using computing technology or software. A virtual environment (VE) is created using this software with a headset, which cognitively stimulates the user's brain to think they are in an artificial world. Creating a VE allows flexibility and measurement of different types of stimuli while recording the various responses provided by users in the controlled VE. VR strengthens the brain's ability to focus, learn, and retain experience. VR for attention deficit disorders has been reported to have promising results. We followed in similar footsteps and designed and

developed a novel, 3D simulated software platform prototype called ReCognition VR to provide VR-based cognitive exercises.

A feasibility clinical trial conducted by our group tested the ReCognitionVR cognitive interventions on older and young healthy volunteers **(Appendix A. Final Study Report).** The results of this study showed that ReCognitionVR-based cognitive exercises were feasible, acceptable, and tolerable by older healthy subjects. In stage 2 of our research study, we want to evaluate the safety, feasibility, acceptability, and tolerability of VR-based cognitive exercises in 60-year-old or older patients following abdominal surgery admitted to the surgical floor at Houston Methodist Hospital (HMH). Our premise is that VR-based cognitive stimulation software will allow the controlled delivery of structured cognitive exercises focusing on orientation, attention, memory, and executive functions. The system will allow customized frequency and duration of cognitive exercises based on the users' difficulty level in a delightfully relaxed-environment with beach wave sounds.

Hypothesis:

We will test the hypothesis that the test population will find ReCognitionVR-based cognitive exercise safe, feasible, acceptable, and tolerable.

2. Purpose of the Study / Objectives

This study aims to assess the feasibility, acceptability, and safety of using ReCognitionVR-based software in older surgical patients. Results from this study will be used to inform the design of a future study in critically ill hospitalized patients at risk for delirium.

The question that drives this study is:
In surgical floor patients, what is the safety and feasibility of using the ReCognition VR-based cognitive exercise, and what is the acceptability and tolerability of the exercise?

OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is the safety of VR-based cognitive stimulation exercises for older surgical patients.	The primary endpoint is the proportion of treatment-emergent adverse events (TEAE) in each group (experimental and control).	1. To assess tolerability of ReCognitionVR-based cognitive stimulation exercises. 2. Adverse events (e.g., cybersickness) will assess tolerability

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		during engagement through exercise provided by ReCognitionVR games.
Secondary		
The secondary objectives are • To assess the changes in vital signs during the exercise • To assess change in vital signs at the end of the exercise	The secondary endpoints are: 1. Mean change from pre to 10 minutes: a. Pulse oximetry oxygen saturation (SpO2) b. Respiratory rate (RR) c. Blood pressure (BP) 2. Mean change from pre to end of VR session: a. SpO2 b. RR c. BP	Knowing the change in these biometric measures will assist in designing future investigations of patients at risk of delirium.
• To assess the feasibility of VR-based cognitive stimulation exercises in older surgical patients.	• using the ReCognitionVR-based cognitive exercise for 20 minutes by 70% of enrolled participants.	It is essential to know if participants can complete the exercise since an incomplete experience will prohibit the assessment of the other variables to be measured.
• To determine the acceptability of VR-based cognitive stimulation exercises	• the proportion of participants with a System Usability Scale (SUS) score >35.	Successful implementation depends on the acceptability of the intervention and is one of the main factors considered before adopting and implementing computerized cognitive software.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
• To determine the accuracy of VR-games • Technical difficulty with VR software	• the proportion of participants who complete the game without any user errors. • Number of attempts to complete the game. • Number of software and device re-starts and re-sets.	Accuracy is an essential variable in assessing the attention of the study subject. Attention is a prominent cognitive domain involved in delirium. Important to upgrade or incorporate advanced VR software.
Exploratory		
Exploratory outcome to report the episode of delirium	• Confusion Assessment Method (CAM) tool (Appendix B)[6] or 4 A's Test score (Appendix C)[7] will be used to assess delirium.	Knowing the proportion of study subjects with new-onset delirium will assist in designing future investigations of patients at risk of delirium.

3. Background

Attention is the most crucial cognitive domain required to effectively complete mentally challenging tasks by healthy individuals. Many healthy people cannot achieve high executive brain functioning tasks due to a lack of focus or attention, leading to poor performance both at work and at home. Generally, mild attention deficit is not identified, and daily life stresses are usually blamed. Computerized cognitive training programs have shown improved attention deficit disorder and mild cognitive impairment. [1] VR is an emerging technology that can improve brain functions, including attention. [2] VR engages multiple learning systems, making it a more effective natural environment for cognitive training. Accuracy in VR games refers to the user's ability to interact with VE accurately, hit targets, and perform tasks. Attention in VR games refers to the user's cognitive focus and engagement in VE. VR provides an immersive experience that can capture a user's attention more effectively than traditional gaming. There is a strong connection between accuracy and attention. When users are more attentive to the game in VE and their tasks, it is likely to improve. The immersive nature of VR encourages the user to be more focused and engaged, enhancing performance in terms of accuracy.

Our group designed and tested a 3D simulated software platform prototype called ReCognition VR with incorporated exercises in the form of games that can improve attention and executive functions. ReCognitionVR- software (Figure 1) allows users to immerse themselves in a relaxing VE; reorient the user to person, time, and location; and play mini-games to encourage attention, focus, and movement of limbs; and record user progress and scores in mini-games.

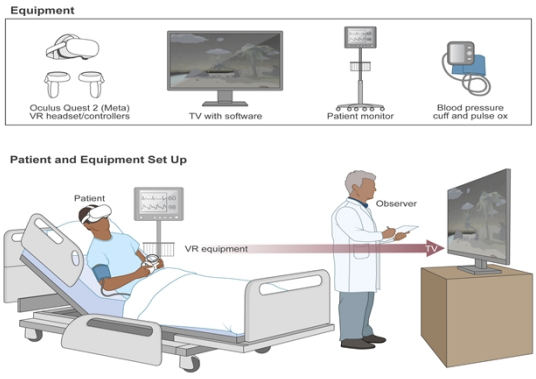


Figure 1: Describes the system architecture to the observer and healthy participants.

Critical gaps exist in our knowledge of cognitive interventions and their application through VR. Data on interventions focused on early cognitive exercise using Virtual Reality Simulation, specifically using Oculus Quest 2 and Unity software, are limited. Moreover, many critical barriers to implementing cognitive training in clinical protocols exist. Cognitive stimulation through VR is a new and upcoming area in technology that is rapidly expanding but is currently limited in literature. A lack of understanding or appreciation for the evidence supporting cognitive stimulation through VR, specifically gamification, contributes to the barriers. The rapid increase and use of VR in other areas urges our team to seek this area for development.

Major goals: This proposal aims to assess the safety/tolerability, feasibility, and acceptability of VR-based cognitive interventions in older surgical patients using ReCognition VR software while providing easy delivery of cognitive stimulation exercises provided by VR.

Preliminary Study:[5] Our group conducted a prospective, single center, randomized, controlled clinical trial in healthy volunteers from August 2021 to December 2022. Healthy volunteers were enrolled based on the American Society of Anesthesiologists (ASA) physical status classification system: **ASA 1** included those aged >18 to 35 years, and **ASA 2** included those aged >60 years. The study results (**Appendix 1: Final Study Report**) were as follows: **Feasibility:** All study participants in both ASA 1 and 2 groups completed the ReCognitionVR-based exercise with feasibility of 100%; **Acceptability/Usability:** The mean SUS scores for ASA 1 and ASA 2 were 88.17±12.83 and 88.67±9.90, respectively There were no statistically significant differences in SUS scores between ASA 1 and ASA 2 (p=0.81); **Tolerability:** Only four adverse events occurred during the study: 3 (20%) in the ASA1 group and 1 (6.67%) in the ASA2 group. Although 1/15 (6.67%) ASA 1 participants experienced transient dizziness and 1/15 (6.67%) ASA 2 participants had a vague undefined mind/brain fog, both participants completed the study interventions. One study participant, 1/15 (6.67%) from the ASA 1 group, experienced a transient increase in SBP >20% from baseline. No participant experienced more than one adverse event. No serious adverse events occurred. The procedure was not interrupted related to an adverse event.

Feasibility and acceptability of ReCognitionVR-based cognitive stimulation in surgical patients.

4. Study Design

The study is a single-center, prospective assessment of the feasibility, acceptability, and usability of ReCognition VR -based simulated cognitive stimulation to improve attention and focus in surgical patients.

Sample size: We will enroll 30 participants: 15 participants who are ≥60 years of age with traditional orientation methods and 15 participants who are ≥60 years of age and receive ReCognitionVR-based cognitive exercises.

Justification of sample size: The study is a feasibility study expecting that 70% of participants in the study intervention group will complete 20 minutes of the ReCognitionVR-based exercise, where each group will be evaluated separately. Descriptive statistics will be used to summarize the findings; 15 participants in each group will be recruited. The intent is that this study will provide information for a larger, subsequent clinical trial of patients ≥60 years old at risk for delirium.

Data and measures to be taken:

The endpoints for this feasibility study are:

Primary Objective:

Safety/Tolerability: We will examine measures that can inform on the safety of the experience to be used in the subsequent clinical trial. The measures are:

1. Mean change from pre to 10 minutes of the ReCognition VR-based exercise in:
    a. SpO2
    b. RR
    c. Blood pressure (Mean BP, Systolic BP, and Diastolic BP)

2. Mean change from pre to end of the ReCognition VR-based exercise in:
    a. SpO2
    b. RR
    c. Blood pressure (Mean BP, Systolic BP, and Diastolic BP)

Secondary Objectives:

Feasibility: 70% of participants in each group will complete 20 minutes of use of the ReCognition VR-based software (a binary outcome).

Acceptability: We will measure the acceptability and usability of the experience based on the proportion of participants with a SUS score >35.

VR-games Accuracy: We will report on the proportion of participants who complete the game without any user errors and the number of attempts each participant uses to complete the game.

Feasibility and acceptability of ReCognitionVR-based cognitive stimulation in surgical patients.

Exploratory Objective:

Delirium: We will assess delirium using CAM tool[6] or the 4 A's test[7]. Delirium is defined as any positive CAM Score or/and score of 4 or above on the 4 A's test for 72 hours after study interventions.

Accessing data from medical records:

Medical records of the potential study subjects will be reviewed for medical history for the inclusion and exclusion criteria described below in section 10.

Data analysis plan:

We will report the demographic variables of age, sex, race, and ethnicity for each group and the clinical characteristics and will review the patient's medical records for body mass index, history of hypertension with active management, drinking status, smoking status, ASA status, pre-existing medical co-morbidities. If not found in the medical record, we will obtain this information.

The results of this study will be reported using descriptive statistics. Continuous variables will be reported as means with standard deviation or medians and interquartile range contingent on the normality of the distribution. Categorical variables will be reported using Chi-square or Fisher's exact test, as appropriate.

5. Study Intervention

1. Older patients (≥ 60 years old) scheduled to undergo abdominal surgeries (open or laparoscopic or robotic assisted), small bowel and large bowel surgery; cholecystectomy; Whipple procedure; pancreatectomy; splenectomy at HMH will be invited to participate.

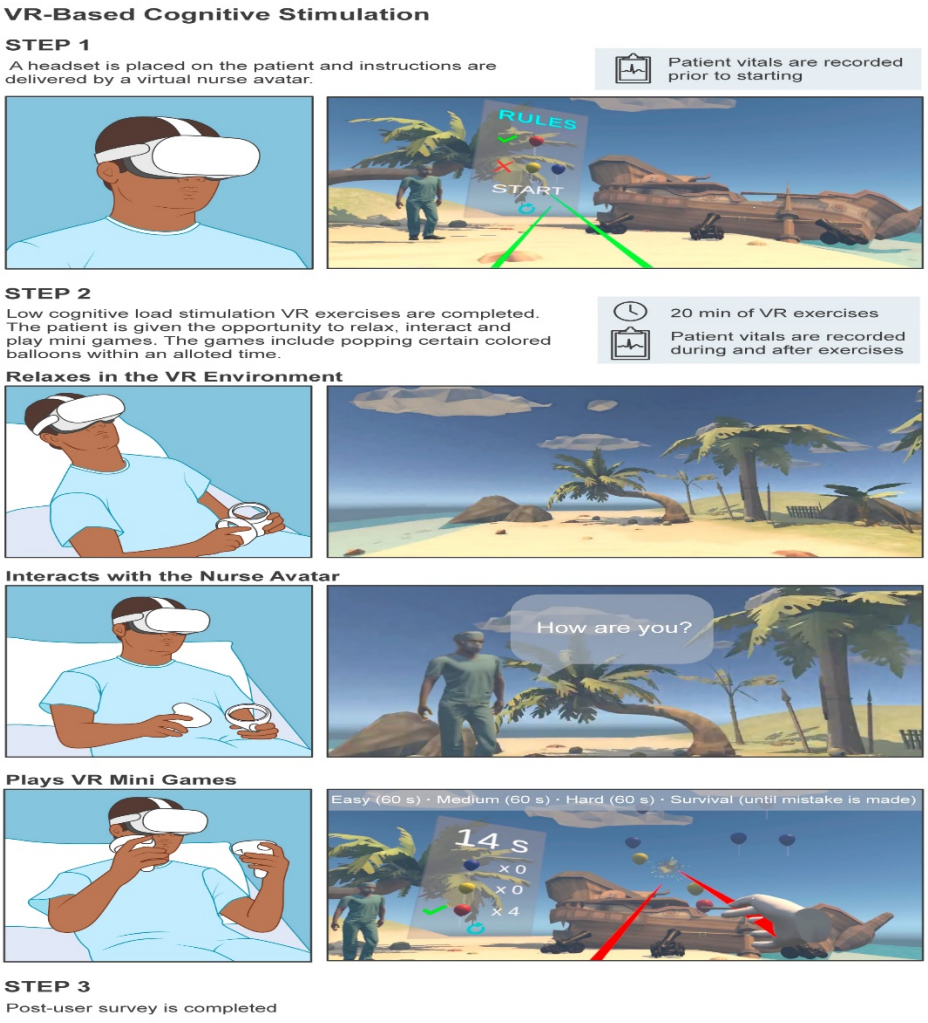
2. We will screen patients for inclusion and exclusion criteria and will assign a screening number.

3. After signing informed consent, participants will be enrolled in the study and randomized using computer-generated randomization software to traditional orientation method (control) or ReCognitionVR-based cognitive exercises (experimental).
4. The experimental group will watch a video on using VR technology, placement of a VR headset, and assessment of baseline cognitive function using the Mini-Cog screening tool.

5. All participants will have a frailty screening assessment.[9]

6. The Mini-Cog screening tool will assess the patient's cognitive status of all participants. (Appendix D)[8]

7. The experimental group will receive a 3D- ReCognitionVR-based simulated cognitive exercise program targeting attention, organizing thinking, and motor activities using VR games. The participant will receive study intervention after arrival to the room from the operating room, free of residual anesthesia, by measuring the Richmond Sedation Scale (RASS)- Appendix – E [10] score of 0.



8. The detail of the software as follows:

   3-D Recognition Virtual Reality-Based Simulation Sessions Program:

   Software Platform:

   The VR platform will consist of

- The VR headsets manufactured by the Oculus Quest 2 glasses (Facebook Inc., USA) with stereoscopic vision and stereo sound will be used to show the virtual world to participants.
- Motion Sensor
- Flat Screen TV with Software

The VR headsets manufactured by the Oculus Quest 2 glasses (Facebook Inc., USA) with stereoscopic vision and stereo sound will be used to show the VR to study participants. After headset placement, the study participants will be able to follow instructions provided by virtual nurse AVATAR. The participants will receive low cognitive load exercises based on virtual reality techniques, including a relaxed environment, music therapy, time orientation, delivery instructions, and task completion motivation. The exercise task will focus on attention, organized thinking, and motor activities.

9. If you are in the traditional orientation method, you will be visited by a nurse at the start of each nursing shift. The nurse will ask you questions to check your memory and attention. Examples of questions include asking you for your name, the date, where you are, and what just happened to you. This will be repeated during every nurse shift change and is the usual care you would receive, even if you were not in the study. In this method, your vital signs (oxygen levels, how fast you are breathing, and your blood pressure) will be measured at different time points after your abdominal surgery as part of your standard care. When you wake up from surgery, you will have the traditional orientation questions asked of you until you are discharged from the hospital. Your participation in this study will be over after you leave the hospital.

Schedule of Activities

Procedures	Screening*	Day 1, Time 1: pre	Day 1, Time 2: 10 minutes	Day 1, Time 3: post	Day 1, Time 4: end of study	Post 24 hours	Post 48 hours	Post 72 hours
Visit number	Visit 0 or 1	Visit 1				Visit 2	Visit 3	Visit 4
Informed consent	X							
Demographics	X							
Medical history	X							
Randomization		X						
Administer study intervention		|----------X----------|						
Concomitant medication review	X							

Procedures	Screening*	Day 1, Time 1: pre	Day 1, Time 2: 10 minutes	Day 1, Time 3: post	Day 1, Time 4: end of study	Post 24 hours	Post 48 hours	Post 72 hours
Visit number	Visit 0 or 1	Visit 1				Visit 2	Visit 3	Visit 4
Physical exam (including height and weight)	X							
Frailty screening assessment	X							
Mini-Cog screening assessment	X							
RASS Score	X							
Pulse oximetry		X	X	X				
Respiratory rate		X	X	X				
Blood pressure		X	X	X				
System User Survey					X			
Number of software and device re-starts, re-sets.		X	X					
Number of User errors			X	X	X			
Number of game attempts			X	X	X			
Adverse event review and evaluation		X	X	X	X	X	X	X
Pain scores (Numeric Pain Scale)	X	X	X	X	X	X	X	X
Positive CAM or/and 4 A's Test	X	X				X	X	X
Complete Case Report Forms (CRFs)	X	X			X			

*Screening Visit and Day 1 may occur on the same day

Feasibility and acceptability of ReCognitionVR-based cognitive stimulation in surgical patients.

Dosing:

The study participants will receive approximately 20 minutes of VR- based cognitive stimulation sessions and complete a post-user survey System Usability Scale.

Acceptability Survey:

Principal Investigator (PI) or a research team member will use the SUS survey to interview the study participants. (Appendix - F)

6. Drugs, Biologics, Devices

Specifically, VR will be simulated using UNITY software and Oculus Quest (two headsets) for this project. The use of ReCognitionVR software is investigational in this proposal. However, in Phase 1a study we evaluated the feasibility, safety, and acceptability of ReCognitionVR software in healthy elderly subjects. The result of the study is uploaded as a clinical study report in MORTI. Moreover, the use of VR software has been approved by FDA. There are multiple VR softwares that are approved by the FDA. Please see the link below for reference:

Augmented Reality and Virtual Reality in Medical Devices | FDA

7. Collaborative / Multi-site Research

N/A

8. Data Privacy / Confidentiality

Houston Methodist policies for Protected Health Information (PHI) will be followed, including all physical and electronic data security requirements, encrypted devices, and HM password-protected servers.

All data obtained for the study will be stored in a password-protected spreadsheet on a Methodist server and will only be accessible to IRB-approved investigators and research staff at Houston Methodist. Data will be completely de-identified at the time of collection and sent to the statistician via secure mail for analysis. Research materials will be stored in a password-protected computer system database on a secure server on the Houston Methodist network. Data collected will be transferred and stored on REDCap®, a secure web application for building and managing databases. Study personnel requiring access will have their Login/Password assigned to the project. Access to clinical study information will be based on individuals' roles and responsibilities. All study data will be transmitted over an encrypted SSL (Secure Sockets Layer) connection that requires user authentication. This application is designed to be in full compliance with the International Conference on Harmonization and Good Clinical Practices

(ICH-GCP), the FDA's Code of Federal Regulations (CFR) 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials," and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Houston Methodist Research Institute (HMRI) policy on record retention will be followed, and human subject research data will be kept for a minimum of 6 years after completing the study. Research written materials will be stored in the Department of Surgery Research Office (Skurlock 1150) and electronic materials on password-protected computer systems on a secure server on the Houston Methodist network.

A unique identification code will be assigned to each participant in this study, and the study team will maintain the linking log with the study files. The only individuals who can see un-coded personal health information include the Study Team and the Institutional Review Board at the hospital, employees of the sponsor who check that this study is being done correctly, and regulatory authorities where required by law.

Data to be collected include:

- Sex
- Age
- Race, ethnicity
- Height, weight
- SpO2 (Time Frame: before, during, and after use of ReCognitionVR software; see Schedule of Activities)
- Respiratory rate (Time Frame: before, during, and after use of ReCognitionVR software; see Schedule of Activities)
- Pain scores (using numeric pain rating scale tool)
- Safety adverse events

Identifier (or parts of)	Recorded	Disclosed	Comment
All elements of dates (except year) for dates directly related to an individual, including patient names, birth date, admission date, discharge date, and date of death; and all ages over 89 and elements of dates (including year) indicative of such age	Yes	No	Necessary for complete data analysis
Phone numbers; Fax numbers	Yes	No	Necessary to complete a questionnaire
Medical record numbers	Yes	No	Necessary to organize data collection

Identifier (or parts of)	Recorded	Disclosed	Comment
Any other unique *identifying* number, characteristic, or code	Yes	No	Virtual cognitive interventions are frequently delivered

9. Data and Specimen Banking

No specimens will be obtained, stored, or banked in this study.

10. Study Population

This study will be a single-center study of older patients who underwent abdominal surgeries and will be conducted at Houston Methodist Hospital. We will enroll 30 patients scheduled to undergo abdominal surgery who are ≥60 years of age. The rationale for enrolling older patients is that older surgical patients are at high risk for the development of delirium.

A total of 30 patients will be prospectively enrolled. 15 patients will receive the standard of care / re-orientation technique, and 15 patients will receive ReCognitionVR-based cognitive exercises. All participants will be given post-use surveys to assess usability and acceptability outcomes.

Inclusion Criteria:

1. Patients ≥ 60 are scheduled to undergo the following abdominal surgeries (open or laparoscopic or robotic assisted) small bowel and large bowel surgery; cholecystectomy; Whipple procedure; pancreatectomy; splenectomy.
2. RASS Score 0

Exclusion Criteria:

1. Subjects with baseline cognitive impairment.
2. Person with active psychiatric disorders and being treated with medications, especially schizophrenia.
3. Person who is deaf or blind.
4. Person with an underlying cognitive disorder or associated phobias (e.g., claustrophobia).
5. Person participating in other clinical trials involving drugs, biologics, devices, or behavioral interventions.
6. Active seizure disorders.

11. Screening and Recruitment

All participants will be screened by the PI and clinical research staff, who have been trained in the clinical investigational plan, to determine if the potential participant is eligible for enrollment. The screening for potential participants will be from within the PI's department. Potential participants will be assigned a screening number which is recorded in an Excel sheet; all participants who receive the study intervention will be noted. All participants must meet eligibility criteria (and if not, which eligibility criteria were not met will be recorded); reasons for not meeting enrollment criteria or receiving study intervention will be recorded. No participants belonging to a vulnerable population will be enrolled.

During the informed consent process, the investigator or designee, who has been trained on the protocol, will explain the nature and scope of the intervention, potential risks, and benefits of participation and answer questions from the potential participants. All participants will sign and date the Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form before any study-specific procedures are performed. In addition, the signed informed consent will be retained with the research records, and a copy will be given to the participant.

Medical records will be reviewed for screening.

12. Withdrawal of Subjects

A participant may discontinue his or her participation without giving a reason at any time during the study. For example, the PI may withdraw a participant due to failure to comply with study intervention requirements, or the participant is uncooperative or refuses to continue in the study intervention. The data from these participants will be retained in the study file and analyzed.

Participants will be withdrawn from the study if they do not receive any study interventions. At the moment of withdrawal, all data related to the participant will be removed from the corresponding Excel documents and waivers will be shredded.

13. Provisions to Protect the Privacy Interests of Subjects

Only the minimum amount of personal information needed to conduct this study will be collected regarding participants' privacy interests. Study participants will be informed that the only individuals who can see un-coded personal health information include the following: the Study Doctor, other employees who work on this study (including the Institutional Review Board) at the hospital, employees of the sponsor who check that this study is being done correctly, and

regulatory authorities where required by law. In addition, participants will be carefully informed about the Release of Health Information section in the Informed Consent Form (ICF), which describes who will access their information and how it will be used. We will emphasize that participation in this study is voluntary and that participants can choose at any time to cease participation and revoke authorization to use and disclose their information.

14. Risks to Subjects

The risks below are associated with the use of the Oculus Quest 2 VR Headset Device.

All adverse events (AEs) will be captured and recorded at each time point. We will report AEs as a proportion of study participants who developed AEs.

Specific AEs to be monitored will include:

Neurological AEs: (Cybersickness is defined as new-onset blurry vision, double vision, dizziness, headaches, eye fatigue, drowsiness, disorientation, and apathy) within 5 minutes after starting the study intervention).

Cardiac Adverse Events: New-onset hypotension (SBP <90 mmHg and DBP <60 mmHg), Bradycardia (HR < 50), Tachycardia (HR> 100), and Arrhythmias (Supraventricular or ventricular) with HR> 150 beats per minutes within 5 minutes after the starting of 3D Simulated VR sessions. Or changes >20% from baselines.

Pulmonary Adverse Events: New-onset hypoxia: SpO2 < 88%, Respirator rate > 35 breaths/minute within 5 minutes after starting 3D Simulated VR sessions.

The safety precautions to minimize the risk to participants are as follows:

- *Vital signs BP*, HR, RR, SPO2, and pain scores (using numeric pain rating scale tool) will be monitored before, during, and after using ReCognitionVR software.
- Mitigation strategy: The gaming environment underwent careful consideration to alleviate cybersickness. We have limited neck motion in the games to avoid sensory conflict, as the subject will remain seated or in a bed during use. Both controllers can still move freely, and the game's design was such that the game could be played from a seated position. In addition, study observers can quickly intervene if a subject begins to feel cybersickness symptoms. The study subjects will be recommended to close eyes and take off the headset until the symptoms subside.

Other Risks

You may be at risk for loss of confidentiality, meaning your information could become known to someone not involved in this study. If this happens, it could result in damage to your reputation, which could also affect your relationships with family and friends, affect your employment, or make it harder to get insurance or a job.

15. Potential Benefits

Direct benefit to participants is not anticipated. The data from this study is expected to inform a subsequent clinical trial of using the ReCognition VR-based software in patients at risk for delirium.

16. Financial and Economic Issues

The participants in this study will not be compensated, and there is no additional cost to participants for taking part in this study.

17. Data Safety Plan

- The research team plans to periodically evaluate data collected regarding the benefits and harms of the study to evaluate the participants' safety.
- Data reviewed periodically will be the following:
    - Adverse effects occurred during the study intervention (dizziness, double vision, disorientation, etc.)
    - Adverse effects during and after the study intervention
    - Delirium on days 1, 2 and 3
- Safety information will be collected during study visits.
- Data collection will occur during the game. Specifically, after the user plays the minigame in the ReCognitionVR Software. Safety data collection will begin before the study intervention and also be collected during and after the study intervention.

All study data will be transmitted over an encrypted SSL connection that requires user authentication. This application is designed to be in full compliance with the International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's Code of Federal Regulations (CFR) 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials," and the Privacy Rule of the HIPAA.

HMRI policy on record retention will be followed, and human subject research data will be kept for a minimum of 6 years after the completion of the study. Research materials will be stored in \ on password-protected computer systems on a secure server on the Houston Methodist network.

The roles and responsibilities of the Investigators are (a) assuring that the trial is conducted according to the Protocol and Manual of Procedures (MOP); (b) identifying, recruiting, and enrolling participants; (c) obtaining informed consent from each participant and protecting their

rights; (d) collecting and entering study data into REDCap, and following participants through study completion: (e) assuring regular IRB/REB review.

18. Informed Consent Documentation and Process

The informed consent will be obtained in written format using a consent document that is HMRI-approved. The investigators involved in the consent process will all be credentialed at HMRI to participate in research at HMH. System Policy and Procedure RE-12 will be followed. The PI and investigators will identify the surgical patient from the surgeon's clinic, pre-anesthesia clinic, and operating room procedures and surgery list. Potential participants may also consent on the same day of use of ReCognitionVR software. During the informed consent process, the investigator or designee, who has been trained on the protocol, will explain the nature and scope of the intervention, potential risks, and benefits of participation and answer questions from the potential participants. All participants must sign and date the Institutional Review Board (IRB) approved informed consent form.

Additionally, the signed informed consent must be kept in the participant's medical records, and a copy must be given to the participant. During the informed consent process, the investigator and designee, who have been trained on the protocol, will explain the nature and scope of the intervention, potential risks, and benefits of participation and answer questions from the potential participants. Participants will be informed that the study is investigational and that their participation in the study is voluntary. They will be informed that they may refuse to participate or may withdraw consent to participate at any time, and for any reason, without jeopardizing their future care at this institution.

The PI and study team will ensure enough time to explain the ICF to the participants and answer all questions before signing the ICF. The study and the contents of the ICF will be explained in detail, and ample time will be given to the study participant to read the consent and discuss it. Questions will be encouraged and will be answered by the participants before the document is signed. The study team will not proceed if adequate time is not available for the participant to demonstrate an understanding of the study and indicate a desire to participate.

19. Waiver of Informed Consent and /or Authorization

No waiver of informed consent or authorization is requested. Medical records will be reviewed.

The study team will require a screening waiver to review the potential patient's medical record for inclusion and exclusion criteria. No PHI will be recorded or stored if the participant does not fit the study eligibility or inclusion criteria. The study team will only collect the minimum necessary information to verify eligibility per inclusion or exclusion criteria. If the participant is

eligible based on the study's inclusion criteria and agrees to participate in the study, then the PI or study team will gain informed consent before collecting any PHI or conducting any study-related procedures.

Waiver of HIPAA Authorization for Research

Complete this section if you will access identifiable health information in a patient's electronic health record or other record held by Houston Methodist Hospital and you are not obtaining a signed authorization from the patient. This waiver can apply to health information accessed to identify potential research participants or for research involving retrospective chart reviews.

1. Purpose of the Waiver:
   - ☐ Chart review study
   - ■ Partial waiver of authorization to identify, prescreen and contact potential participants.
   - ☐ Alteration of the requirements for a HIPAA Authorization to remove the signature. *
   - ☐ Other Please explain

Note if the IRB waives the signature requirement, the participant must receive a copy of the HIPAA authorization language.

2. Provide protocol-specific responses to the following items that describe why the waiver is being requested for the use of PHI in this research.

   a. The IRB must find that the use/disclosure of protected health information (PHI) involves no more than minimal risk to the privacy of individuals. Please select the safeguards your team will use to meet this requirement.

   - ■ Electronic safeguards, such as password protection, data encryption, and institution firewall, will be used to protect PHI
   - ■ Physical safeguards, such as locked cabinets, locked filing room, secure, locked office area, will be used to protect PHI

☐ The study team will record only anonymous data or coded data that are linked to the participants' identity through a file that is separate from the data.

■ Administrative safeguards such as policies and procedures, staff education on the HIPAA Privacy Rule.

☐ Other: ____

c. Describe why the research cannot practicably be conducted without the waiver or alteration of patient authorization to use PHI in research

■ Access to and use of PHI is necessary to obtain information of potential subjects.

☐ The number of screen failures is anticipated to be high for this research and access to the PHI to confirm potential study eligibility will prevent unnecessary contact with potential participants.

☐ Too many participants will be lost to follow up or will not answer the request for an authorization to conduct the record review study.

☐ Other: ____

d. Describe why the research cannot practicably be conducted without access to and use of

the PHI:

☐ The study team will access the minimum PHI necessary to contact potential participants to assess their interest and eligibility.

■ The study team will access the minimum PHI necessary to prescreen for eligibility and to contact potential participants to assess their interest.

■ The study team will access the minimal PHI necessary data elements to answer the research question.

3. Identify

List the identifiers you will record.

■ Name

■ Address (all geographic subdivisions smaller than state, including street address, city county, and zip code)

■ All elements (except years) of dates related to an individual (including birthdate, admission date, discharge date, date of death, and exact age if over 89)

- [x] Telephone number
- [ ] Fax number
- [x] Email addresses
- [ ] Social Security Number
- [x] Medical record number
- [ ] Health plan beneficiary number
- [ ] Account number
- [ ] Certificate or license number
- [ ] Vehicle identifiers and serial numbers, including license plate numbers
- [ ] Device identifiers and serial numbers
- [ ] Web URL
- [ ] Internet Protocol (IP) Address
- [ ] Finger or voice print
- [ ] Photographic image - Photographic images are not limited to images of the face.
- [ ] Any other characteristic that could uniquely identify the individual

By submitting this request for waiver of patient authorization, I certify:

(1) That the identifiers will be destroyed at the earliest opportunity consistent with the conduct of the research as defined by federal, state, and/or local laws and regulations.

[x] The PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.

20. References

1. Rizzo, A. A., Buckwalter, J. G., Bowery, T., Van Der Zaag, C., Humphrey, L., Neumann, C., et al. (2000). The virtual classroom: a virtual reality environment for the assessment and rehabilitation of attention deficits. *Cyber Psychol. Behav.* 3, 483–499. doi: 10.1089/10949310050078940doi: 10.1002/14651858.CD008349.pub4
2. Lee E, Kim J. Cost-benefit analysis of a delirium prevention strategy in the intensive care unit [published online ahead of print, 2014 Oct 29]. *Nurs Crit Care*. 2014;10.1111/nicc.12124. doi:10.1111/nicc.12124.
3. Turon M, Fernandez-Gonzalo S, Jodar M, et al. Feasibility and safety of virtual-reality-based early neurocognitive stimulation in critically ill patients. *Ann Intensive Care*. 2017;7(1):81. doi:10.1186/s13613-017-0303-4.
4. Gang Li, Joaquin A. Anguera, Samirah V. Javed, Muḥammad Adeel Khan, Guoxing Wang, Adam Gazzaley; Enhanced Attention Using Head-mounted Virtual Reality. J COGN NEUROSCI 2020; 32 (8): 1438–1454. doi: https://doi.org/10.1162/jocn_a_01560
5. Usability, Acceptability, and Safety of Virtual Reality-based Cognitive Intervention. ClinicalTrials.gov Identifier: NCT05583903. Usability, Acceptability, and Safety of Virtual Reality-based Cognitive Intervention - Full Text View - ClinicalTrials.gov.
6. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941-948.
7. Evensen S, Hylen Ranhoff A, Lydersen S, Saltvedt I. The delirium screening tool 4AT in routine clinical practice: prediction of mortality, sensitivity and specificity. Eur Geriatr Med. 2021 Aug;12(4):793-800.
8. Borson S, Scanlan JM, Chen PJ et al. The Mini-Cog as a screen for dementia: Validation in a population-based sample. J Am Geriatr Soc 2003; 51:1451–1454.
9. Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc. 2008;9(2):71-72.
10. Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S et al. Monitoring sedation status over time in ICU patients: the reliability and validity of the Richmond Agitation Sedation Scale (RASS). JAMA 2003; 289:2983-2991.