PROTOCOL TITLE:

Usability and acceptability of virtual reality-based cognitive stimulation by healthy participants

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REVISION HISTORY

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

1. Study Summary

Virtual reality (VR) imitates reality by creating an artificial 3-D environment using computing technology or software. Using this software with a headset, a virtual environment is created, which cognitively stimulates the user's brain to think they are in an artificial world. Creating a virtual environment allows flexibility and measurement of different types of stimuli while recording the various responses provided by users in the controlled virtual environment. VR strengthens the brains' ability to focus, learn, and retain experience. VR for attention deficit disorders has been reported to have promising results. We plan to follow in similar footsteps using the gamification of exercises for cognitive stimulation in healthy volunteers to record outcomes and usability testing.[1] These exercise "games" allow users to focus and pay attention to the game while helping reorient and cognitively stimulate the user's brain. The games are built with increasing difficulty and complexity of user demand and output. Our team developed a

novel, 3D simulated software platform prototype called ReCognition VR to provide VR-based cognitive exercises to healthy participants for testing.

Our premise is that VR-based cognitive stimulation software will allow 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 music.

Hypothesis:

We will test the hypothesis that VR-based cognitive exercise will be feasible and acceptable by the test population.

2. Purpose of the Study / Objectives

The purpose of this study is to determine the feasibility, acceptability and usability, and to assess the safety of use of a VR-based software in health volunteers. Results from this study will be used to inform the design of a future study in hospitalized patients at risk for delirium.

The question that drives this study is:
In healthy volunteers, what is the feasibility of use of the ReCognition VR-based software and what is the acceptability and usability of the software?

OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is to assess the feasibility of VR-based cognitive stimulation exercises in healthy volunteers.	The primary endpoint is use of the ReCognition VR-based software for 20 minutes by 70% of enrolled participants.	It is important to know if participants can complete the exercise since an incomplete experience will prohibit assessment of the other variables to be measured.
Secondary		
The secondary objectives are • to determine the acceptability and usability of VR-based cognitive stimulation exercises	The secondary endpoints are: • Acceptability and usability: 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

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• Proportion of participants who complete the game without any user errors • Number of attempts to complete the game.	implementing computerized cognitive software.
Tertiary/Exploratory		
Tertiary objectives are to report the safety of VR-based cognitive stimulation exercises in healthy volunteers.	• Safety will be assessed using each of the following endpoints: 1. Mean change from pre to 10 minutes: a. Heart rate variability: b. Pulse oximetry oxygen saturation (SpO2) c. Respiratory rate d. Blood pressure 2. Mean change from pre to end of VR session: a. Heart rate variability: b. Pulse oximetry oxygen saturation (SpO2) c. Respiratory rate d. Blood pressure	Knowing the proportion of change in these biometric measures will assist in designing future investigation of patients at risk of delirium

3. Background

Attention is the most crucial cognitive domain required for the effective completion of mentally challenging tasks by healthy individuals. Many healthy people cannot complete high executive brain functioning tasks due to lack of focus or attention, leading to poor performance both at work and 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. Virtual Reality (VR) is an emerging technology and can improve brain functions, including attention. VR engages multiple learning systems, making it a more effective natural environment for cognitive training. Based on this idea, our team developed a 3D simulated software platform prototype called ReCognition VR with incorporated exercise in the forms of games that can improve attention and executive functions.

Recognition VR software (Figure 1) allows users to immerse themselves in a relaxing virtual environment; 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.

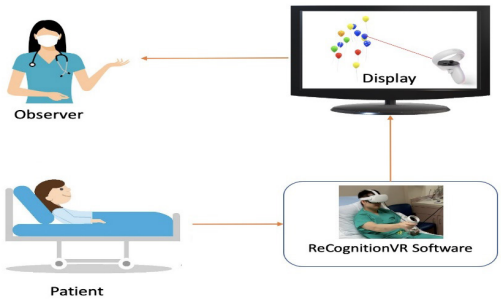

Figure 1: Describes the system architecture to the observer and healthy participants

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 exercise in clinical protocols exist. Cognitive stimulation through VR is a new and upcoming area in technology that is rapidly expanding but currently limited in the 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.

The major goals of this proposal are to assess the feasibility and usability of VR-based cognitive interventions in healthy volunteers using ReCognition VR software while providing easy delivery of cognitive stimulation exercises provided by VR.

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 healthy participants.

Sample size: We will enroll 30 participants: 15 participants who are >18 or up to 35 years of age and 15 participants who are >60 years of age. Results from each age group will be analyzed separately.

Justification of sample size: The study is a feasibility study having the expectation that 70% of participants in each group (>18-35 years of age and >60 years of age) will complete 20 minutes of the ReCognition VR-based exercise and 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 – 70% of participants in each group will complete 20 minutes of use of the ReCognition VR-based software (a binary outcome).

Secondary – We will measure the acceptability and usability of the experience based on the proportion of participants with a System Usability Scale (SUS) score >35.

We will report on the proportion of participants who complete the game without any user errors

We will report on the number of attempts each participant uses to complete the game.

We will examine measure that can inform on 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. Heart rate variability:
    b. Pulse oximetry oxygen saturation (SpO2)
    c. Respiratory rate
    d. Blood pressure
2. Mean change from pre to end of the ReCognition VR-based exercise in:
    a. Heart rate variability:
    b. Pulse oximetry oxygen saturation (SpO2)
    c. Respiratory rate
    d. Blood pressure

We will report the demographic variables of age, sex, race and ethnicity for each group and the clinical characteristics whereby they meet ASA criteria (body mass index, self-reported history of hypertension with active management, drinking status, and smoking status; see Section 9).

Accessing data from medical records:
This feasibility study involves healthy volunteers. No medical records will be reviewed. Medical history will be self-reported.

Data analysis plan:
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 normality of the distribution. Categorical variables will be reported using Chi-square or Fisher's exact test, as appropriate.

5. Study Intervention

1. The healthy participants will be selected from a random population to use the Recognition VR – based cognitive exercise interventions.
2. The study participants will receive a 3D- ReCognition VR-based simulated cognitive exercise program targeting attention, organizing thinking, motor activities, and executive brain functions.
3. The study team will create an order set for the 3-D Recognition VR – based cognitive stimulation exercise sessions to be delivered to the healthy participants who will place virtual reality headsets on themselves.
4. The detail of the software as follows:

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

Software Platform:

Virtual reality platform will consist of

- The virtual reality 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 virtual reality headsets manufactured by the Oculus Quest 2 glasses (Facebook inc., USA) with stereoscopic vision and stereo sound will be used to show the virtual reality 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, motor activities, and executive brain functions.

Dosing:

The study participants will receive approximately 20 minutes of VR- based cognitive stimulation session and fill out a post-user survey.

The session will provide neurocognitive stimulation, engagement through exercise.

The physiological data of vital signs will be recorded before, during, and after sessions (see Schedule of Activities).

Acceptability Survey:

PI or a research team member will interview the healthy participants using the System Usability Scale survey.

The estimated date to complete the study is one month after the last participant is enrolled.

Schedule of activities

Procedures	Day 1, Time 1: pre	Day 1, Time 2: 10 minutes	Day 1, Time 3: post	Day 1, Time 4: end of study
Informed consent	X			
Demographics	X			
Medical history	X			
Administer study intervention	|----------X----------|			
Concomitant medication review	X			
Physical exam (including height and weight)	X			

Procedures	Day 1, Time 1: pre	Day 1, Time 2: 10 minutes	Day 1, Time 3: post	Day 1, Time 4: end of study
Frailty assessment	X			
Heart rate variability	X	X	X	
Pulse oximetry	X	X	X	
Respiratory rate	X	X	X	
Blood pressure	X	X	X	
System User Survey				X
Adverse event review and evaluation				X
Complete Case Report Forms (CRFs)	X			X

6. Drugs, Biologics, Devices

Specifically, VR will be simulated using UNITY software and Oculus quest (two headsets) for this project.

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 in 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 own Login/Password. 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).

HMRI policy on record retention will be followed, and human subject research data will be kept 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. 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
- Heart rate variability & heart rate variability analysis (Time Frame: before, during, and after use of RecognitionVR software; see Schedule of Activities)
- Pulse oximetry oxygen saturation (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)
- 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, 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
Any other unique *identifying* number, characteristic, or code	Yes	No	Virtual cognitive interventions frequency delieverd

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 healthy volunteers conducted at Houston Methodist Hospital. We will enroll 15 participants who are >18 and <35 years of age and 15 participants who are ≥60 years of age. The rationale for the age distribution is to obtain information from people who are considered healthy by ASA criteria 1 and people who meet ASA criteria 2. Partcipiants who are >18 to 35 years of age are a) more likely to have experienced VR software previously and b) more likely to meet ASA criteria 1. Participants who are >60 years of age are a) less likely to have experienced VR software previously and b) more likely to meet ASA criteria 2 . These older participants are considered similar to the target population of a proposed subsequent inventional clinical trial; however, it is possible that participants in the younger age group (>18 to 35 years of age) may meet ASA crtieria 2.

A total of 30 participants will be prospectively enrolled. All participants will be given post-use surveys to assess usability and efficacy outcomes.

Inclusion Criteria:

1. Healthy volunteers >18 years of age who meet one of the following criteria:
    a. ASA 1: A normal healthy patient. Example: Fit, nonobese (BMI under 30), a nonsmoking patient with good exercise tolerance.
    b. ASA 2: A patient with mild systemic disease. Example: Patient with no functional limitations and a well-controlled disease (eg, treated hypertension, obesity with BMI under 35, frequent social drinker, but is nonsmoking).
2. Person without underlying cognitive disorder or associated phobias (eg. claustrophobia).

Exclusion Criteria:

1. Person with active psychiatry disorders, especially schizophrenia
2. Person who is deaf or blind.

11. Screening and Recruitment

All participants will be screened by the principal investigator and clinical research staff, who have been trained in the clinical investigational plan, to determine if the potential participant is eligible for enrollment. Potential participants will be assigned a screening number which be recorded in an excel sheet; all participants who receive the study intervention during the 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 enrollmente 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.

Healthy Participants will be identified:
1. Through public advertisement sent via flyers posted around Texas Medical Center and mass emails to public domain emailing lists for example, University of Houston and Rice University, available to the local Houston population.

No medical records will be reviewed for this healthy volunteer study. Medical history obtained will be from participant self-report.

12. Withdrawal of Subjects

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

A participant may discontinue his or her participation without giving a reason at any time during the study. For example, the Principal Investigator may withdraw a participant due to failure to comply with pilot study intervention requirements, or the participant is uncooperative or refuses to continue in the study intervention.

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 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 Virtual Reality 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: (defined as new-onset blurry vision, tingling, perioral numbness, seizures, or coma within 30 minutes after starting the study intervention)

Cardiovascular AEs: (defined as new-onset hypotension [SBP <90 mmHg and DBP <60 mmHg], bradycardia [HR < 50 bpm], tachycardia [HR >130 bsspm], or any new hemodynamic instability requiring more than two vasopressors after starting the study interventions

Pulmonary AEs: (defined as new-onset hypoxia [SpO2 < 88%] and/or hypercarbia [PCO2 > 60 mmHg] on arterial blood gas within 30 minutes of starting study interventions

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 the starting of 3D Simulated VR sessions.

Others: Rash, nystagmus, muscular hypertonicity, clonus or myoclonic jerks, and allergic reactions

If enrolled participants vital signs changes > 20% from baseline, the session will be stopped as it would be considered unsafe events

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.

15. Potential Benefits

No direct benefit to participants is anticipated. The data from this study is expected to inform on a subsequent clinical trial of the use of 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 in order to evaluate the safety of the participants
- Data reviewed periodically will be the following:
    - Accuracy of the game/outcome
    - Adverse effects occurred during study intervention (ex. Seizures, nystagmus etc.)
    - Adverse effects post-24 hours of study intervention
    - Number of software and device re-starts and re-sets.

- Safety information will be collected during study visits and through telephone calls with participants

- Data collection will occur during the game. Specifically after the user plays the minigame in the ReCognitionVR Software. The software has been programmed to report the outcome to the research team once the user plays the minigame. Safety data collection will begin before the study intervention and also be collected 24 hours after study intervention.

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).

HMRI policy on record retention will be followed, and human subject research data will be kept 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 (a) assuring that the trial is conducted according to the Protocol and 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

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 healthy participants through public and randomized advertisement. 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 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. 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 to the participant's before the document is signed. The study team will not proceed if adequate time is not available to 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. No medical records will be reviewed. Participants will self-report their medical history. No PHI will be recorded or stored if the participant does not fit 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.

20. References

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