STUDY PROTOCOL

PROTOCOL TITLE:
Virtual Reality Cognitive Training for Mild Cognitive Impairment: a Pilot Feasibility Study

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PRINCIPAL INVESTIGATOR:
Kua Zhong Jie Zaylea, Clinical Psychologist, Changi General Hospital

1 BACKGROUND AND RATIONALE

As a global public health priority, there has been a pressing demand for the development and deployment of novel interventions to prevent and delay the onset of dementia. In recent years, Computerized Cognitive training (CCT) has garnered considerable evidence in improving the cognitive outcomes of individuals living with Mild Cognitive Impairment (MCI), a transitional stage between normal aging and dementia. The aim of this pilot study is to assess the feasibility and efficacy of CCT, specifically a multi-domain Virtual Reality Cognitive Training (VRCT) program on the cognition of individuals with MCI. The VRCT program will be conducted weekly over a period of 10 weeks for participants aged 65-85 with a diagnosis of MCI. 30 participants will be recruited from specialist outpatient clinics and they will be randomized into either the VRCT intervention group or the active control group. All participants will be assessed at baseline and post-intervention. We hypothesize favorable acceptability of the VRCT program. We also postulate positive changes on neuropsychological measures of attention, processing speed, memory and executive function following program completion. We expect these gains in cognition to be translated to improvements on secondary outcomes including mood and self-reported everyday memory functioning. In CGH, there is currently a lack of follow-up intervention options for patients who have received a diagnosis of MCI. Usual care procedures would include medication for risk factors as well as health advice for lifestyle factors such as exercise, diet and cognitively stimulating activities. If outcomes from this study prove to be positive, it will add to the evidence base of the novel application of Virtual Reality technology to Cognitive Training in a clinical setting. Furthermore, this will provide clinicians in CGH with an innovative intervention option to meet the needs of MCI patients in maintaining and enhancing their cognitive functions.

1.1 General Introduction

Over the last four decades, global prevalence of dementia has increased exponentially, with regions including Latin America, North Africa and Southeast Asia having a proportionately higher acceleration in prevalence as compared to other world regions[1]. As one of the leading causes of disability and dependency in old age, dementia poses tremendous socioeconomic impacts to healthcare systems worldwide, with medical, social care and informal care costs estimated at US$604 billion annually[2]. In Singapore, the population of older adults has also seen dramatic growth: from 2.5% of the population in 1965 to 13.7% in 2018[3]. This has brought about an increase in the number of people diagnosed with dementia, currently found to be at 10% for older adults aged 60 and above[4].

1.2 Rationale and Justification for the Study

Mild cognitive impairment (MCI) is a symptomatic transitional stage between normal aging and dementia, where individuals display objective evidence of cognitive impairment but still maintain functional and social independence[5]. An estimated 10% to 55% of MCI cases progress into dementia over a 2- to 6-year time period[6]. Given the disability and distress associated with worsening cognition, growing efforts have been made to prevent or delay the progression of MCI to dementia. With an absence of approved pharmacological options to treat the underlying pathophysiological mechanisms of MCI, increasing attention has been placed on lifestyle modifiable factors and non-pharmacological interventions to target the cognitive symptoms[8].

A non-pharmacological intervention that has garnered interest and considerable evidence in recent years is Computerized Cognitive Training (CCT). CCT involves guided repetitive practice of standardized

tasks designed to target specific cognitive skills or processes, with the aim of improving cognition via reinforcement of neural pathways[9]. Accessibility to cognitive training is enhanced with the use of technology, particularly for older adults whose mobility may be limited. The computerized features also enable a more individualized approach where activities may be tailored to the users' ability levels, thereby improving user engagement. The efficacy of CCT has been rigorously reviewed in recent meta-analyses of randomized control trials which reported cognitive benefits in both cognitively healthy older adults and patients with mild cognitive impairment[10,11]. Notably, the overall effect size of CCT on cognition was found to be higher for individuals with MCI ($g = 0.35$) as compared to individuals with dementia ($g = 0.28$)[11] as well as healthy older adults ($g = 0.22$)[10], indicating the use of CCT as a viable intervention for enhancing cognition in people with MCI.

1.2.1 Rationale for the Study Purpose

Among the various types of CCT interfaces that are currently available, including computer/tablet-based programs and videogames, Virtual Reality (VR) technology is the most recent and novel application of CCT. As compared to its traditional counterparts, the wrap-around display screens of VR systems offer the added advantage of a simulating and immersive environment that produces a sensation of "presence" or "being there". VR systems also afford a versatile experimental platform that can provide timely feedback to clinicians regarding patient progress via real-time monitoring of the system performance[12]. Evidence for the efficacy of VR on health-related outcomes has been demonstrated in other clinical populations including cognitive rehabilitation for patients of traumatic brain injury[13] and exposure therapy for patients with anxiety and phobic disorders[14]. While the evidence base for VR application on MCI patients is currently still limited, available research suggests its utility in enhancing treatment adherence and cognitive outcomes of MCI patients. In a study examining the effects of an attentional task on selective and sustained attention, participants with MCI were exposed to two task conditions – a highly realistic image-based rendered VR condition and a paper version of the task. Not only did participants endorse a preference for the VR interface over the paper condition, apathetic participants reported greater preference for the VR condition than non-apathetic participants, indicating VR's potential in improving adherence to cognitive training[15]. One study had developed a 6 months VR memory training (inclusive of 3 months training phase and 3 months booster phase) for nursing home residents with memory deficits[16]. The authors found significant improvement in memory test scores, especially in long-term recall, for participants in the intervention group whereas those in the control group demonstrated progressive decline in their memory functions[16]. These positive results in the memory domain are supported by another study which examined the efficacy of memory and balance training VR program on participants with MCI[17]. Finally, even among MCI participants of Chinese ethnicity, VR seems to be acceptable and efficacious, with the VR group showing greater improvement in objective memory performance post-training than the non-VR group[18].

While other VR programs have largely focused on a single cognitive domain, we aim to assess the effects of a broad-based VRCT program that targets multiple cognitive outcomes. As compared to single-domain CT intervention, multi-domain CT appeared to be more advantageous in maintaining treatment effects[19]. Notably, two high quality randomized controlled trials have demonstrated interesting neuroimaging outcomes where increases in hippocampal functional connectivity were observed following multi-domain CCT, which is postulated to prevent memory loss[20]. To our knowledge, this research would be the first of its kind in Singapore, thereby contributing to the current evidence base on the efficacy of VRCT on enhancing the cognition of individuals with MCI. In the clinical setting, MCI patients in Changi General Hospital are offered a limited range of treatment and follow-up options after receiving their diagnosis due a lack of available interventions. Through this pilot feasibility study, we hope to introduce an innovative clinical service to target the cognitive health of our patients with MCI. We believe that the current feasibility study will provide us with useful information

in guiding us to conduct a randomized controlled trial for a VRCT group program as well as a longitudinal study in the future to evaluate the effects of VRCT in delaying the progression of MCI to dementia. We hope that this novel intervention will improve our clinical service, efficiency and reduce manpower needed to run cognitive interventions for our patients.

1.2.2 Rationale for Study Design

This is a pilot feasibility study using a parallel design where participants are randomized into either the Virtual Reality Cognitive Training (VRCT) intervention group or the active control group.

2 HYPOTHESIS AND OBJECTIVES

This pilot study aims to assess the feasibility and effects of a Virtual Reality Cognitive Training (VRCT) program on the cognitive function of older adults with Mild Cognitive Impairment (MCI).

2.1 Primary Objectives

Our primary objective is to (1): assess the retention and adherence rates of the VRCT intervention and (2) examine effects of VRCT on cognition, everyday memory performance and mood of older adults with MCI.

2.2 Potential Risks and Benefits:

2.2.1 Potential Risks

The use of VR equipment for an extended period of time may induce a dizzy feeling in older adults. In order to prevent this, we limit the duration of VR usage to under 30 minutes. We will also check in with our participants in regular intervals to assess their comfort levels. Participants with severe visual or hearing impairment will be excluded from this study.

2.2.2 Potential Benefits

Participants are expected to report improvements in cognitive functioning and mood after the program.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be Enrolled

As this is a pilot study, there is no power calculation for the sample. Based on the funding available, we intend to recruit up to 30 participants.

3.2 Criteria for Recruitment and Recruitment Process

The participants will be recruited from outpatient clinics in Changi General Hospital, referred by geriatricians and psycho-geriatricians.

3.3 Inclusion Criteria

- Aged 65-85
- Diagnosis of MCI by a clinician in accordance to Petersen's criteria
- Ability to see and hear
- Ability to read and write in either English or Mandarin
- Mini-Mental Status Examination > 23

3.4 Exclusion Criteria

- A primary other neurocognitive disorder
- Major psychiatric illness such as major depressive disorder or anxiety disorder
- Severe visual or auditory impairment
- Serious medical illnesses including acute or severe asthma, severe or unstable cardiovascular disease, active gastric ulcer, severe liver disease or severe renal disease

3.5 Subject Replacement

Participants who complete at least 8/10 sessions of VRCT will be included in the study. Dropouts will not be replaced.

4 STUDY DESIGN

This is a pilot feasibility study using a parallel design where participants are randomized into either the Virtual Reality Cognitive Training (VRCT) intervention group or the active control group. Study recruitment would be completed in approximately 3 months. Participants are expected to be involved in the study for no more than 12 weeks each.

4.1 Randomisation and Blinding

A biostatistician, independent of our research, will generate the random allocation sequence. Sealed envelopes will be used to conceal the random allocation sequence. Researchers will enrol the eligible participants and assign them to either the intervention or control group by following the sequence allocation. A Clinical Research Co-ordinator who is blinded to the group assignments will be conducting the outcome measures.

4.2 Study Visits and Procedures

4.2.1 Screening Visits and Procedures

All patients who have received a diagnosis of MCI and achieved a cognitive screening score of MMSE > 23 will be informed about the research by their primary physician when they attend their regular outpatient clinic visits. If patients were to express interest, the treating physicians will then seek patients' consent to be referred to the study team. Upon receiving the referral, researchers will then obtain permission from the primary physician to contact these patients about the purpose, procedures, risks and benefits of the study. If patients were to endorse their agreement over the phone, an invitation

letter will be mailed to potential participants to come to the hospital for consent-taking as well as undergo pre-intervention neuropsychological testing.

4.2.2 Study Visits and Procedures

For Virtual Reality Cognitive Training Intervention Group:

Visit 1 (Week 1): Pre-intervention neuropsychological testing (2 hours)
Visit 2-11 (Weeks 2-11): Virtual Reality Cognitive Training (50 minutes per session)
Final Visit (Week 12): Post-intervention neuropsychological testing (2 hours)

For Active Control Group:

Visit 1 (Week 1): Pre-intervention neuropsychological testing (2 hours)
Visit 2 & 3 (5 weeks apart): Psychoeducation and Cognitive Stimulation (1 hour per session)
Final Visit (Week 12): Post-intervention neuropsychological testing (2 hours)

During the VR session and cognitive training, frequent checks will be perform to ensure that subject is comfortable. Should subject expressed fatigue or discomfort, session can be stopped and resume when subject is able to continue. The number of breaks will be recorded.
Appointment between session will be at least 7 days apart.

4.2.3 Post Study Follow up and Procedures

Participants will be offered treatment as usual of cognitive rehabilitation or cognitive stimulation should they wish to follow up on cognitive interventions for their MCI.

If the current study results prove to be promising, participants in the active control group will also be offered the VRCT intervention.

4.3 Discontinuation/Withdrawal

4.3.1 Discontinuation Criteria

The study will be discontinued for participants who continuously complain of discomfort and dizziness in using the Virtual Reality equipment.

4.3.2 Discontinuation Visit and Procedures

If voluntary withdrawal occurs, participant will be asked to complete the self-report questionnaire to access intervention acceptability and to collect feedback on the program.

5 TRIAL MATERIALS

5.1 Trial Product (s)

Virtual Reality (VR) System
The VR experiences are administered through a head-mounted Oculus Go Screen V7. The hard-ware specifications are as follows:

- Oculus Go Screen: 5.5-inch display with a 2560 x 1440 resolution (1280 x 1440 per eye)
- Oculus Go Processor: Qualcomm's Snapdragon 821 processor from

- Oculus Go Weight: 468 grams

The VR system runs on a software developed by Dancing Mind Pte Lte. The software specifications and service provided by Dancing Mind Pte Ltd include:

- MindGym System Functions: System Setup (Processor Setup, Password Changing etc)
- Data Centre (Memory Care Therapy Data Analytics Report Querying and Printing Functions)

To ensure infection control, all equipment will be sanitized with alcohol wipes after use.

6 TREATMENT

6.1 Rationale for Selection of Dose

The VRCT Program

Participants will undergo 50 minutes of weekly VRCT sessions over an 10-week intervention period. The program consists of three components: (1) psychoeducation on cognitive functioning and ways to maintain cognitive health, (2) VR cognitive training tasks and (3) VR relaxation modules. The cognitive training tasks are designed to target cognitive performance on domains including attention, working memory, memory and executive functions. These tasks require participants to: (1) remember placement and order of pictures in a specific timeframe, (2) identify and recall commonly seen objects, (3) identify 3D moving objects without being distracted by messages, (4) strategize route to escape a maze under time constraints etc. Psychologists who are conducting the program will monitor participants' individual progress. Task difficulty is continuously adjusted based on participants' performance. The VR relaxation modules consist of mindfulness and meditation activities designed to enhance mental well-being.

6.2 Blinding

Participants will be informed in the participant information sheet that if they were to agree to participate in the study, they will be randomized either to the VRCT group or active control group.

6.3 Concomitant therapy

Participants assigned to the active control group will undergo two hourly sessions of psychoeducation on cognitive health and cognitive stimulation activities. They will also be given a cognitive stimulation kit consisting of puzzles and games and provided with a weekly guide to engage in these intellectual activities weekly at home.

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

7.2 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the clinical trial. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

7.3 Safety Monitoring Plan

The data and safety monitoring would be performed by the principal investigator and co-investigators. The data would be reviewed monthly or at the point of recruitment of every 10 subjects, whichever occurs first. Data that would be reviewed would include adverse events occurring during the intervention such as excessive patient agitation resulting in injuries or device dislodgements requiring terminal of intervention.

15 subjects would be receiving intervention. If 8 or more subjects are unable to meet the composite end-point for completion of intervention, the study would be terminated.

7.4 Complaint Handling

Complaints would be informed to the principal investigator and discussed with study co-investigators. Should the complaint be unrelated to the study, the participant's primary physician would be informed. Should the complaint be related to the study involving patient safety and welfare, CIRB would be notified.

8 DATA ANALYSIS

8.1 Data Quality Assurance

Data entered into the electronic databases will be routinely reviewed for the purposes of tracking the progress of the study, assuring accuracy, and completeness of the data. Adverse events or serious adverse events will be recorded and monitored to ensure the safety of the participants.

8.2 Data Entry and Storage

All hardcopy research data will be stored in a cabinet with lock and key access.
All softcopy research data will be stored in a password protected PC.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

As this is a pilot study, there is no power calculation for the sample. Based on the funding available, we intend to recruit up to 30 participants.

9.2 Statistical and Analytical Plans

Intention-to-treat analyses will be performed using the last observation carried forward method for subjects who were lost to follow-up or had missing data. Data will be analysed using IBM SPSS Statistics 26.0. Continuous variables will be presented as mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate, while categorical variables will be presented as frequencies and percentages. A one-way analysis of variance will be conducted to assess the between-group difference of the intervention's effect over time for each outcome measurement. The significance level will be established at $p < 0.05$. Cohen's d effect size (ES) will be reported alongside the p-values, and thresholds of 0.2 for small, 0.5 for moderate, and 0.8 for large effects were employed as guiding benchmarks.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigators will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Study related personnel will be trained by the study team on the protocol, proper use of data collection form, informed consent procedures, randomization, maintenance of essential study documents and any other study procedures such as study assessments, before study initiation.

The study-trained investigator or study coordinator may conduct any additional training of study centre personnel after study initiation.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and

regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

Consent process will be undertaken and obtained before the initiation of the study. The consent process will be undertaken in a quiet room in the outpatient clinic. To prevent coercion or undue influence, informed consent will be by a Study Team Member who is not the primary physician of the participant. Both the Mini-Mental Status Examination and clinical judgement made by primary physician will be utilized to determine an individual's mental capacity. Individuals with a major neurocognitive disorder will be excluded from our study.

12.2 Confidentiality of Data and Patient Records

All hardcopy research data will be stored in a cabinet with lock and key access.
All softcopy research data will be stored in a password protected PC. All data will be coded with an identifier. The key to the code will be stored in a separate computer.

13 PUBLICATIONS

Results of the current study belong to the study team members. Acknowledgements will be given to the sponsors including the CGH Innovation Grant and Dancing Mind Pte. Ltd. for sponsoring a free headset and licensing during our study.

14 RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained by the PI in a secure storage facility. The records will be accessible for inspection and copying by authorized authorities. Data will be kept for 7 years before secure destruction.

15 FUNDING and INSURANCE

This project has been awarded with the CGH GY2019/20 Innovation Grant amounting to $20000. Upon completing of the project, the PI is required to submit a written final report and present the findings as required by the CGH Office of Innovation.

16 Results Summary

Participants in the VRCT group exhibited significant favourable changes in the RBANS figure copy ($p = 0.01$) and FAB go-no-go ($p=0.04$) subdomains over time as compared to the control group (Table 3). While not statistically significant, moderate to large ES favouring the VRCT group were observed in RBANS list recall (ES = 0.7) and RBANS figure recall (ES = 0.8). Small to moderate ES favouring the VRCT group were demonstrated in FAB (ES = 0.3), and FAB conflicting instructions (ES = 0.3).