



BMJ Open Effects of biophilic virtual reality on cognitive function of patients undergoing laparoscopic surgery: study protocol for a sham randomised controlled trial

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ABSTRACT

Introduction Virtual reality (VR) is already being used for cognitive or emotional rehabilitation. However, its role in postoperative cognitive dysfunction (POCD) has not been fully recognised. Due to the lack of an effective postoperative follow-up system, the incidence of POCD in China is not clear, and although many drugs have been proposed to improve POCD in the animal study, their clinical applications are limited, while VR provides an innovative method to provide non-pharmacological management.

Methods and design This is a single-centre, randomised, double-blind, sham-controlled clinical trial. In this study, 600 patients over 55 years old undergoing laparoscopic surgery will be recruited. Participants will be randomly assigned to receive biophilic VR or sham VR (1:1 ratio), all patients have 20 min of exposure per day during the hospital stay. The primary outcome is the impact of VR on the incidence of POCD. Secondary outcomes include perioperative anxiety and instrumental activities of daily living. Changes in the performance of the neurocognitive batteries are measured by a local resident doctor. Serum samples will be collected on the day before surgery and 7 days after surgery.

Ethics and dissemination This trial has ethical approval from the Medical Ethics Committee of the Affiliated Hospital of Medical School of Ningbo University (KY20210302). The study is sponsored by Ningbo University and Ningbo Science and Technology Bureau. Contact: Dr. Mao Haijiao, Chair of the hospital medical Ethics committee (ndfylvunli@126.com). Trial results will be submitted for publication in peer-reviewed journals, patient recruitment began in April 2021. Written informed consent is obtained for all participants. All information acquired will be disseminated via national or international conferences and published in peer-reviewed journals.

Trial registration number ChiCTR2000040919.

INTRODUCTION

Postoperative cognitive dysfunction (POCD) refers to disorders of mental processes that

Strengths and limitations of this study

- ⇒ This is a prospective, randomised clinical trial, which provides the best clinical evidence and support for virtual reality (VR) as an intervention to bring down the incidence of postoperative cognitive dysfunction within 1 year.
- ⇒ This study integrates subjective cognition scale into the follow-up cognitive batteries.
- ⇒ This is a single-centre study, the result may not apply to other institutions;
- ⇒ The content of VR may not be the focus of interest to all the participants.

occur from 30 days after anaesthesia and surgery to 1 year after surgery, which can lead to long-term dementia or decline in cognitive functions, such as verbal or visual memory loss, language comprehension or visuospatial disabilities.¹ Studies have shown that POCD occurs in 15%–30% of elderly patients over 65 years of age.² Notably, POCD could last for weeks or months,³ significantly reducing the quality of life of patients postoperatively. Even though some patients with POCD do not feel difficulty with thinking and memorising, instrumental activities of daily living (IADL) such as shopping, using the toilet, and dressing are somewhat affected.⁴ A strong correlation between POCD within 12 months after coronary artery bypass graft surgery and patient's death within 10 years was observed,¹ and the incidence of dementia in POCD patients increased significantly (up to 30.8%) at 7.5 years after surgery,⁵ which caused a huge economic burden to families and society.

Despite increasing multidisciplinary collaboration in the clinical environment, there

is currently no single anaesthetic technique, drug or monitoring modality that could reduce the incidence of POCD.⁶ As the pathogenesis of POCD is still not clear, and there is a lack of therapeutically effective drugs in the clinic, much attention has been paid to nonpharmacological interventions due to their ability to reverse the neurodegeneration and decline of cognitive function in elderly patients.⁷ Meanwhile, the enriched environment could attenuate learning or memory disorders and neurogenesis impairments after surgery by stabilising brain-derived neurotrophic factor (BDNF) expression.⁸ However, for patients who have undergone laparoscopic surgery, it takes time for the internal environment to recover, and facilitating cognitive rehabilitation by the means of short-term provision of a dynamic enriched environment is not easy to achieve.

Why biophilic virtual reality?

Studies have shown that virtual reality (VR) training increases neuronal activity in the prefrontal lobe and improves patients' cognitive behaviour,⁹ and nowadays VR is gradually used in the rehabilitation training of patients with neurodegenerative diseases, such as patients who had a stroke as well as patients with chronic neglect.¹⁰ As VR does not require patients to get out of bed for aerobic exercise, it is well suited for rehabilitation of postoperative cognitive function. The biophilic VR can simulate the green space outdoors in nature and has the effects of improving the creativity of office personnel and reducing stress and anxiety for people with substance use disorder.¹¹ Furthermore, it is reported that exposure to surrounding greenness was associated with better scores on tests of attention for children in a longitudinal cohort.¹² Whether the perioperative use of biophilic VR could improve the cognitive function of patients undergoing laparoscopic surgery remains unknown. In the clinical setting, POCD is usually diagnosed based on the patient's complaint and the change of neuropsychological scale score.³ However, a traditional scale like a Mini-Mental State Examination is considered not sensitive enough to detect changes in cognition, compared with other imaging methods, like Fluoro-2-deoxy-D-glucose PET (18F-FDG) PET,^{13 14} while the latter one is expensive and radioactive. Clinicians are expecting novel biomarkers, yet few studies could achieve long-term postoperative tracking and evaluation of patients, as well as observe the impact on cognition by perioperative biophilic VR intervention, we will apply the method of Montreal Cognitive Assessment (MoCA) test as recent study suggested that the 2 scores rule with MoCA had the best combination of sensitivity and specificity to diagnose delayed neurocognitive recovery.¹⁵

A prospective, randomised, clinical trial is designed to assess the efficacy of biophilic VR to decrease the incidence of POCD and the severity of anxiety in patients undergoing laparoscopic surgery. We hypothesise that biophilic VR will be more effective at reducing anxiety and incidence of POCD in this population than a sham control.

Outcome measures

Primary

- ▶ To find the incidence of POCD for major laparoscopic surgery within 1 year.
- ▶ To investigate the effectiveness of biophilic VR in reducing the severity of cognitive decline following major laparoscopic surgery.

Secondary

- ▶ To investigate the incidence of subjective cognitive decline (SCD) for major laparoscopic surgery within 1 year.
- ▶ To examine the correlation between postoperative cognitive changes and neuronal injury biomarkers.
- ▶ To identify the role of perioperative anxiety in the development of POCD.
- ▶ To assess participants' VR visual discomfort symptoms.

Hypotheses

Primary

That administration of biophilic VR in the perioperative setting is superior to sham for reducing the incidence of POCD, which will be measured by changes in performance on the modified IADL and telephone-MoCA (T-MoCA) within 1 year.

Secondary

Neurovascular changes in a certain part of the brain may be consistently associated with the occurrence and severity of POCD.

- ▶ That administration of biophilic VR in the perioperative setting is superior to sham for reducing the severity of anxiety.
- ▶ That administration of biophilic VR in the perioperative setting is superior to sham for reducing serum levels of biomarkers of inflammation and neurofilament light (NFL) chain in the postoperative phase.

Methods and design

A single-centre, randomised, sham-controlled clinical trial. A total of 600 participants are randomised into either a blank or biophilic VR group in a 1:1 ratio.

Study setting

This study will be conducted in the affiliated hospital of medical school of Ningbo University, which is a public tertiary teaching hospital.

Regulatory approval

The human research ethics committee from the affiliated hospital of medical school of Ningbo University has provided ethical approval (KY20201105).

Participants

We are recruiting 600 adults (300 per group) more than 55 years undergoing laparoscopic surgery. Experienced research nurses will identify and contact potential participants in the preoperative clinic. Prospective participants will be given an information and consent form, which

must be signed and witnessed by a member of the research team before registration. Participants' postoperative visits will be conducted through a local resident doctor who was born and raised in Ningbo since the majority of patients communicate using the Ningbo dialect.

Inclusion criteria

Patients aged 55 years or older who are undergoing major laparoscopic surgery, defined as surgery expected to last more than 2 hours in duration and requiring seven nights stay in hospital. This criterion is similar to another International Study of POCD.¹⁶

Exclusion criteria

1. An expected lifespan of less than 3 months.
2. An MoCA score of less than 24.
3. A history of dementia or psychiatric illness.
4. Current use of sedatives, antidepressants or corticosteroids.
5. Alcoholism and drug dependence; History of chronic pain.
6. Serious hearing and vision impairment and not being able to read.
7. Difficulty with follow-up or poor compliance.

Randomisation, allocation and concealment

Recruitment began on 1 April 2021, and will be finished by the end of April 2024.

Each patient will be provided with a detailed explanation of the procedure and the goals of the study. Once the patients who underwent laparoscopic surgery sign the research informed consent, they will be randomly assigned to a biophilic VR treatment group or a sham VR group. Randomisation will be performed by following a computer-generated list. Allocation will be made by using sequentially numbered sealed envelopes with information disclosing the type of procedure to be applied. A total of 600 patients will be randomly assigned. The assignment code will be hidden from all the experimenters except the research nurses who apply VR headsets to the patients. The research nurse will not participate in the data collection. All other relevant personnel, including investigators, research assistants, and participants, will turn a blind eye to treatment allocation before the end of the data analysis. To hide the therapy, all VR devices look the same shape and colour. Additionally, the sham VR group will also have a light background music set. The size and appearance of the device for the two groups are the same. All VR glasses will be returned to the ward after the discharge of the patients for review. According to the identified risk factors, age stratification enhances equality among groups in terms of the impact on cognition.¹⁴

Trial procedures

This is a single-centre, prospective, randomised clinical trial of patients undergoing laparoscopic surgery to assess the impact of biophilic VR sessions on the incidence of POCD. [Figure 1](#) summarises the study design. Participants in this trial procedure will receive initial recruitment and

basic neurocognitive and psychological screening interviews (MoCA, IADL scores, self-rating anxiety scale and subjective cognitive scale). Venous blood (5 mL) will be drawn before anaesthesia and 7 days after surgery for measuring biomarkers possibly related to POCD.

Interventions

All patients will use the same VR device and software (Shurui healthcare company, Guangzhou, China). This biophilic VR device is commercially available and is not Food and Drug Administration regulated. It is an all-in-one headset with no additional hardware. A set of headphones, included with the headset, is used to deliver audio instructions and sound, creating a fully immersive experience. Patients will be encouraged to undergo two sessions every day with the VR headset for up to 7 days after surgery: 9:00 hours in the morning and three pm in the afternoon. This daily exercise is divided into 10 min in the morning and 10 min in the afternoon, which is a recommended frequency for mind-body therapies.^{17 18} Biophilic VR device will be dispensed by the research nurses in the ward, and recorded in the sharable electrical trial records for each participant. Episodes of nausea and dizziness are recorded by research staff, and participants will have a 2 min break if he or she feels dizzy; the Virtual Reality Symptom Questionnaire (VRSQ) evaluation will be adopted, and if the patient has a score of VRSQ more than five after the intervention, he or she will drop out the cohort, and we will use both the strategy of intention to treat and per-protocol to deal with the data.

Biophilic VR

After the admission procedure, the participants will receive VR intervention. The period of biophilic VR exposure is based on the studies by Liao *et al.*¹⁹ and Yin *et al.*²⁰ with minor modification, that is twice a day, once at 9 o'clock in the morning and once at 3 o'clock in the afternoon, 10 min each time. The contents of biophilic VR are a 360° view with two scenarios playing in random order: one is a space of green mountains and clear water, and the other is a rainforest at sunset. Patients could sit in the ward and look around, but they are not encouraged to walk around in case of falling. Natural music in the background is mixed with the sound of gurgling streams and birds singing. Blood pressure and heart rate will be measured and recorded with a monitor before and after VR intervention. The patients will receive VR therapy throughout their stay in the hospital.

Sham VR

The sham VR is set as a control, it simulates an ordinary indoor environment under incandescent lamps without natural scenes. The background music is the same as biophilic VR. Blood pressure and heart rate will be measured and recorded with a monitor before and after VR intervention. The patients will receive VR therapy throughout their stay in the hospital.

Mood disorder measurement

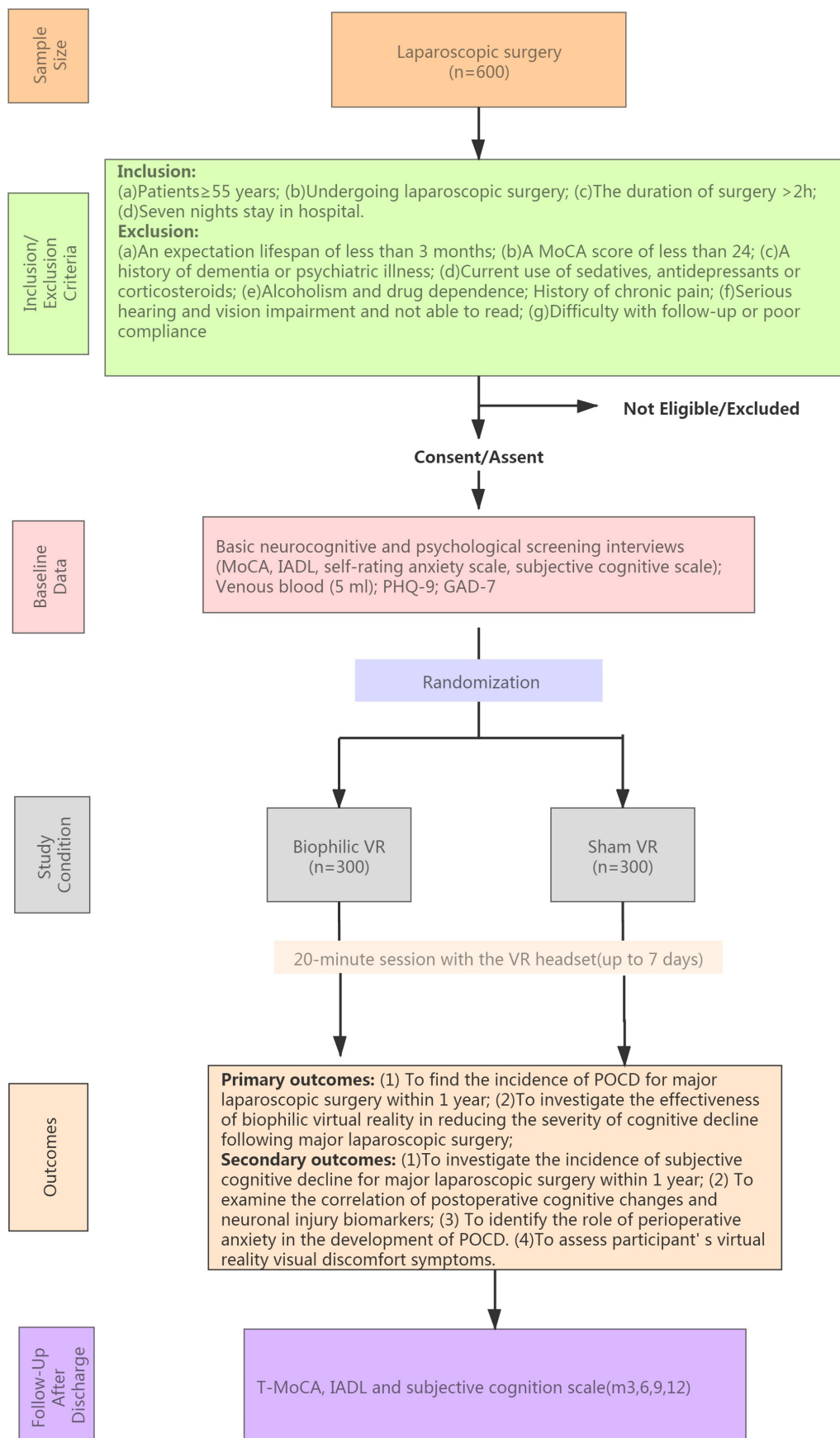


Figure 1 Study flow chart (CONSORT Diagram). CONSORT, Consolidated Standards of Reporting Trials; IADL, instrumental activities of daily living; MoCA, Montreal Cognitive Assessment; POCD, postoperative cognitive dysfunction; VR, virtual reality.

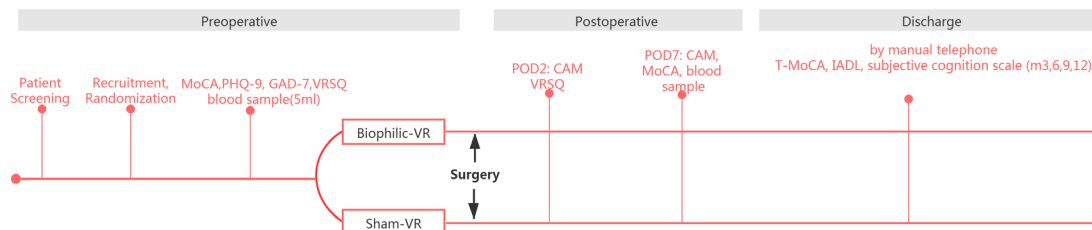


Figure 2 Experimental design of the study. CAM, Confusion Assessment Method; GAD-7, Generalised Anxiety Disorder-7; IADL, instrumental activities of daily living; MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire-9; POD, postoperative day; T-MoCA, telephone-MoCA; VR, virtual reality; VRSQ, Virtual Reality Symptom Questionnaire.

‘Depression and Anxiety’ will be assessed right after admission as well as the day before surgery using the self-report questionnaire: Patient Health Questionnaire-9 and Generalised Anxiety Disorder, GAD-7.

Delirium assessment during the hospital stay.

Delirium will be assessed on POD 2 and POD 7 using the short form of the Confusion Assessment Method instrument (CAM).²¹

Cognitive function measurements by a local physician.

SCD and IADL will be used to measure cognitive function after discharge from the hospital. Meanwhile, on the first day of the 3rd month, 6th month, 9th month and 12th months after the operation, a modified telephone interview for cognitive status (T-MoCA) will be applied with previous batteries postoperatively. Our team aims to extend the duration of observation of postoperative cognition change of patients with laparoscopic surgery by manual follow-up and drawing more comprehensive conclusions through the integrated batteries. [Figure 1](#) and [figure 2](#) summarise the experimental design.

Blood biomarkers of inflammation and neuroaxonal injury

Blood samples (5 mL) will be collected by the researchers and rotated in equal proportions into separate plasma, serum and whole blood fractions. Then it will be stored in the fridge at -80°C to prepare for the analysis at the end of data collection. Although surgery and anaesthesia are associated with systemic inflammatory response, patients with POCD tend to show higher levels of inflammatory markers, including interleukin-1 β (IL-1 β) and IL-6 compared with patients with complete cognitive function.^{16 22} Similarly, markers of neurogenesis will also be detected, for example, the association of the plasma neuroaxonal injury markers NFL and incidence of delirium is noted recently, yet potential predictive biomarker for long-term cognitive decline need further evidence.²³

Outcome variables

Primary outcome

Between-group comparison of cognitive performance in the late postoperative period (within 1 year), as measured using the modified telephone interview for cognitive status (T-MoCA) and SCD change. POCD will be defined in an individual when the score of MoCA is decreased by 2.^{24 25} Since these modified telephone scales covered

more than two cognitive domains, the Z-score will be used based on the total score of the scale.

Secondary outcomes

Between-group comparison of mood disorder improvement in the preoperative period, as measured using the HPQ-9, GAD-7.

- ▶ Between-group comparison of physical activities, as measured using the IADL during the first year after surgery. Comparisons to raw score obtaining at presurgical baselines will be made every other 2 months.
- ▶ Between-group comparison of delirium, as measured using the CAM, on days 2 and 7 after surgery. Incidents of delirium will be recorded by nurses.
- ▶ Between-group comparison of potential blood biomarkers: NFL chain and neuroinflammatory factor (IL-1 β , IL-6).

Withdrawal and adverse events report

Participation is entirely voluntary and consent may be withdrawn at any stage. Withdrawal reasons are documented and recorded. Participants will not be considered to have withdrawn if they are lost to follow-up, and research staff will attempt to reconnect with participants for subsequent assessments. For example, a participant who is unable to be contacted for the 3-month follow-up is regarded as a missed session, but research staff will attempt to contact the participant for the 12-month follow-up. Participants are withdrawn from treatment and/or assessment if they:

- ▶ Withdraw consent for participation.
- ▶ Are unblinded for any purpose before the end of the treatment period.
- ▶ Require unplanned surgery or anaesthesia prior to measurement of the primary outcome variable.

Data collection and storage

Graphite document is a real-time online collaboration synchronisation tool, our local institutional review board (IRB) will check the data at the end of every 2 months. All the data of those eligible participants will be collected and the electronic medical record will be extracted in a standard format. We will use the Dryad repository to store all the original data in our research.

Sample size determination

PASS V.11 software will be used to evaluate the number of participants. According to the previous literature, the incidence of POCD is 29%,²⁶ assuming that a 10% decrease in incidence in the VR intervention group as an effective intervention, $\alpha=0.05$, POWER=0.8, the sample size is 283. Taking into account the possible loss of follow-up rate of 5%, the actual sample required for clinical inclusion will be around 600.

Missing or incomplete data

All participants recruiting into the study, regardless of treatment group, are to have as much data as possible recorded, as fully as possible following this protocol. Missing data will be monitored to avoid bias by attrition or patterns of missing data. All cases of missing data, including lost to follow-up of participants or withdrawal of consent, will be recorded by research staff. The time point, the frequency and reasons for missing data are to be recorded. Missing data will be examined to see if there are patterns informative to the study; for example, if certain variables are missing systematically by an identifiable pattern of participants

Safety

It is anticipated that the risk to participants in this study is minimal. The specific VR device used in this study is a minimal risk device. We will minimise nosocomial infection risks by using disposable medical wipes every time after patients finish intervention. Patients will explicitly be instructed to remove the headset when any side effects or discomfort occurs. The PI will continually monitor all risks to the participants. Weekly clinical meetings will be used to address quality assurance and safety concerns with the study.

Trial status

The trial began recruitment in April 2021. The study will be conducted under the principles of ethics and good clinical practice detailed in the declaration of Helsinki and the International Coordination Conference.

Patient and public involvement

Patient safety is our top priority in the whole process of intervention. We will spend abundant time introducing the VR device and making sure every participant knows how to wear it properly. There are no patients or anyone in the public involved in the design, recruitment or conducting of this study. Our institutions will use VR in the perioperative period for data collection and information gathering. Participants may receive information about any study results if they wish by writing a letter to the principal investigator. We will share access to the full protocol to requesting individuals/institutions.

Data analysis

For quantitative data, before analysis, a person unrelated to the study will add anonymous codes to all data sheets to guarantee that the research team and statistician

are blinded to group allocation when processing and analysing the data. Data distribution will be investigated using Q-Q plots, cross-tabulations and histograms. Data on participant characteristics, outcome measures, recruitment, retention, fidelity (eg, actual VR play time and number of interruptions), and feasibility of delivering the interviews (eg, number and quality of telephone calls) will be summarised using descriptive statistics such as mean, SD, median, IQR and frequencies as appropriate.

For qualitative data, another independent research secretary who understand local Ningbo dialect will determine the feasibility, acceptability and safety of the intervention, interviews will be analysed using the five iterative stages of the Framework Analysis method (familiarisation, thematic framework identification, indexing, charting, mapping and interpretation), All audio files and interviews will be additionally backed up in a computer file with code.

Statistical analysis will be done with IBM SPSS Statistics V.21 (IBM SPSS). Group comparisons will be made using independent t-tests for continuous variables, Mann-Whitney U test for ranked data, and χ^2 or Fisher exact test for dichotomous data. All hypothesis testing will be two-tailed. A p value of less than 0.05 will be taken to indicate significance. The modified Poisson regression procedure and 95% CIs will determine individual tests and combined outcomes. Ethics and Dissemination.

Ethics

This trial has ethical approval from the Medical Ethics Committee of the Affiliated Hospital of Medical School of Ningbo University (KY20210302). The trial will be conducted in full conformance with the principles of the Declaration of Helsinki. The experiment will also follow the Ningbo University Research Integrity Guidelines. Trial results will be submitted for publication in peer-reviewed journals, patient recruitment began in April 2021. Written informed consent is and will be obtained for all participants. To participate in the experiment, all participants will voluntarily give their informed permission. Additional informed consent will be acquired from persons chosen at random to engage in postoperative interviews over the phone.

Dissemination

In consultation with the Ethic Committee, a thorough distribution plan will be prepared early in the trial. The findings of the study will be distributed to all participants as well as those who intended to participate but did not match the inclusion criteria and requested feedback on the results.

The trial's findings will be published in a peer-reviewed journal and presented at national and international perioperative brain health and VR conferences. For pilot and feasibility studies, the trial shall be reported in accordance with the Extended Consolidated Standards of Reporting Trials statement. The International Committee

of Medical Journal Editors guidelines will be used to determine authorship.

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Contributors BZ is responsible for drafting the manuscript. JW and WQ are the principal investigators, provide specialist knowledge and have overseen protocol development. WL and QW assisted the selection of neurocognitive assessments and training in administration, and interpretation of results. JL, AH and HX assisted the interpretation of data, GB and ZY provided considerable expertise in the use of biophilic virtual reality, research design, assessment timing, research coordination and investigation of serum samples. QW and ZY selected the timing and is responsible for the investigation of serum samples. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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