

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

# **BMJ Open**

# Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-083966
Article Type:	Protocol
Date Submitted by the Author:	04-Jan-2024
Complete List of Authors:	Liang, Surui; Shenzhen Hospital of Southern Medical University, Department of Nursing Tian, Jinfei; Shenzhen Hospital of Southern Medical University, Intensive Care Unit Liu, Yong; Shenzhen hospital,Southern medical university, ICU Wen, Taoxue; Shenzhen Hospital of Southern Medical University, Intensive Care Unit Luo, Dan; Shenzhen Hospital of Southern Medical University Cai, Wenzhi; Shenzhen Hospital of Southern Medical University,
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, INTENSIVE & CRITICAL CARE, Virtual Reality
	T.



**BMJ** Open

Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing
 Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol
 ABSTRACT

4 Introduction:

This is the first randomized controlled trial (RCT) designed to evaluate the effects of a Virtual Reality-based sensory stimulation intervention on preventing delirium in intensive care unit (ICU) patients.

8 Methods and Analysis:

We employed a paired randomization method to match eligible participants based on a validated delirium risk scoring model for ICU patients. A consecutive sample of 324 ICU patients admitted to the study setting will be recruited. Eligible participants will be randomly allocated to receive either Virtual Reality-based sensory stimulation in addition to usual care or usual care alone. The Virtual Reality-based sensory stimulation intervention will last for up to fourteen days, with all interventions administered by a research team. The primary outcomes will include delirium incidence, duration, and severity. The secondary outcomes will encompass patients' psychological well-being (post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes, and other outcomes (quality of life, independence, and cognitive function). Data will be collected at baseline, post-intervention, and six months post-intervention. Paired-sample t-tests or paired Wilcoxon signed-rank tests, Kappa consistency tests, or McNemar's tests will be used for categorical variables. The study will adhere to the intention-to-treat principle for analysis. Mixed-effects models will be used to analyze differences between groups in delirium duration, delirium severity, psychological outcomes, and other outcomes. 

**Discussion:** 

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

1	The results will provide valuable information for stakeholders considering the integration of
2	Virtual Reality-based sensory stimulation into routine nursing practice.
3	Ethics and dissemination This protocol was approved by Research Ethics Committee of
4	Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068). All participants
5	will provide written informed consent. Results will be disseminated through scientific
6	publications, and presentations at local and international conferences.
7	Trial registration number ClinicalTrials.gov NCT06153472. Trial registration date:
8	November 22, 2023
9	Word counts: 232
10	Keywords: Critical care; Delirium, Virtual Reality, Sensory stimulation
11	
12	Article Summary
13	Strengths and limitations of this study
14	► This study evaluates a Virtual Reality-based sensory stimulation for preventing
15	delirium and improving patients' psychological well-being (specifically post-traumatic stress
16	disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length
17	of stay), and other outcomes (such as quality of life, independence, and cognitive function).
18	► To the best of the authors' knowledge, this is the first initiative to incorporate a
19	Virtual Reality-based sensory stimulation intervention for preventing delirium in ICUs.
20	► Due to the nature of the intervention, blinding was only possible for the outcome
21	assessors, while blinding for the participants and those delivering the intervention was not
22	feasible.
23	
24	
25	
26	

#### BMJ Open

### INTRODUCTION

Delirium is a common acute state of cognitive confusion. Intensive Care Unit (ICU) delirium is highly prevalent, with an incidence ranging from 31%(1) to 56%(2), and it can be as high as 81%(3) in ICU patients undergoing mechanical ventilation. A preliminary analysis of data from 375 patients admitted to the ICU for more than 24 hours revealed an occurrence rate of 44% for ICU delirium(4). Moreover, delirious ICU patients had 1.33 times longer ICU stays and a 9.57-fold increase in mortality compared to non-delirious ICU patients(5). ICU patients who experience delirium may suffer from post-traumatic stress disorder, anxiety, depression, and cognitive impairment for up to two years(6).

Non-pharmacological preventive measures aim to reduce one or more modifiable risk factors for ICU delirium(7). Previous research identified sensory stimulation as a key and effective non-pharmacological intervention in preventing ICU delirium(8,9). Sensory stimulation involves activating one or more senses(10), with visual and auditory stimuli being particularly effective for ICU patients(11). To further investigate the effectiveness of sensory stimulation in preventing ICU delirium, the research team conducted an initial study to assess the implementation of sensory stimulation on preventing delirium in ICU and subsequently developed a sensory stimulation intervention plan(12,13). This plan involved daily sessions of 30 minutes each for seven days, including visual stimuli (displaying personal or family photos) and auditory stimuli (playing recordings of family members). The results of the study showed that sensory stimulation reduced the duration and severity of ICU delirium but did not significantly decrease the incidence of ICU delirium(8,9). The limited effectiveness of sensory stimulation may be attributed to the narrow range of stimuli, insufficient stimulus intensity, and inadequate dosing and implementation methods(9).

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

In contrast, Virtual Reality (VR) technology, characterized by its three-dimensional and highly immersive qualities, has the potential to provide more effective sensory stimulation by immersing participants in three-dimensional dynamic environments(14). International research conducted internationally suggests that VR offers significant advantages in sensory stimulation and could be a promising approach for preventing ICU delirium. However, it's important to note that studies on the use of VR in preventing ICU delirium are currently in the feasibility testing stage(15–17). The DREAMS project at the University of Florida in the United States investigated the effectiveness of VR and found that 95.6% of participants found it very comfortable, 51.9% reported improved sleep quality, and 81.5% experienced reduced pain(16). This team further conducted a study with 46 ICU patients, implementing a seven-day VR intervention, which resulted in reduced stress, pain, anxiety, and improved cognitive function and attention in the participants (17). Additionally, Jawed and colleagues conducted a preliminary trial that showed VR could alleviate anxiety in ICU patients(15). However, since those studies were in the feasibility testing stage, they were unable to measure the effects on reducing ICU delirium.

The stress recovery theory and attention restoration theory explain the principles behind preventing ICU delirium using VR-based sensory stimulation(18,19). The stress recovery theory suggests that natural environments support positive changes in emotional states and psychophysiological recovery, primarily by relaxing the parasympathetic nervous system (19). In stressful ICU environments, cognitive and attentional resources can become fatigued, which is especially crucial for critically ill patients facing stressors. The cognitive demands and overstimulation in the ICU environment contribute to mental fatigue and stress responses. On the other hand, the attention restoration theory suggests that exposure to natural environments

#### **BMJ** Open

requires fewer cognitive resources and promotes a sense of disengagement from stressors, allowing attention to rest and recover(18). Therefore, VR-based visual and auditory stimuli, by immersing patients in relaxing VR environments, can have a protective effect against environmental stress and aid in the recovery of physiological, emotional, and attentional functions, thus preventing delirium. Chirico and colleagues further elucidated the mechanisms of VR-based sensory stimulation in delirium prevention: exposure to VR-based natural environments can trigger a specific psychophysiological pattern activated by the parasympathetic nervous system, leading to intense emotional reactions. Emotion responses increase with higher levels of immersion, which can be utilized to alleviate symptoms like anxiety, pain, and fear, effectively reducing patient stress, improving sleep quality, and consequently reducing the incidence of delirium(20).

### Aim and hypothesis

This study aims to evaluate the effects of evaluates a Virtual Reality-based sensory stimulation on preventing delirium and improving patients' psychological (post-traumatic stress disorder, sleep quality, ICU memory), patients' clinical (ICU length of stay) and other outcomes (quality of life, independence and cognitive function). It is hypothesised that at patients' fourteenth day of ICU hospitalisation or the day of discharge (if the ICU stay is less than 14 days), will experience the following improvements compared with those receiving usual care.

- 1. ICU patients receiving the sensory stimulation intervention will have:
  - a. A greater reduction in incidence, duration and severity of delirium.
  - b. A significant improvement in their post-traumatic stress disorder.
  - c. A significant improvement of factual memories.
  - d. A shorter length of ICU stay.

e. A significant improvement in quality of life, independence and cognitive function.

At six months after completing the intervention, compared to those receiving usual care,

ICU patients undergoing the VR-based sensory stimulation intervention will experience a significant improvement in quality of life, independence, and cognitive function.

# **METHODS AND ANALYSIS**

# Design

An assessor-blinded two-arm RCT will be conducted. Figure 1 shows the study flow.

# Setting

Participants will be recruited from general ICUs of two comprehensive tertiary A -level hospitals in Shenzhen, Guangdong province, Mainland China. Tertiary A-level hospital provides specialist tertiary care in a large hospital after a referral from primary and secondary care.(21)

# Participants

All ICU patients admitted to the study setting will be recruited if they are/have: (1) aged 18 years or older, (2) first-time admission to the ICU, and (3) a Richmond Agitation-Sedation Scale (RASS) score of  $\geq$ -3(22). Patients will be excluded if they have: (1) been diagnosed with dementia, delirium or acute psychiatric illness at admission, (2) been diagnosed with end-stage cancer, (3) severe hearing impairment and cannot be corrected by hearing aids and (4) been admitted to ICU with radioactive material.

# Sample size determination

Sample size calculation for the difference test in delirium incidence between the experimental and control groups was performed using G\* Power 3.4. Based on a prior study, delirium incidence after sensory stimulation was 13%, while it was 25% in the standard care group, yielding an odds ratio of 0.57(8). For G\* Power's two-sample proportion (McNemar) calculation, the study established a significance level of  $\alpha = 0.05$  and a test power of Power =

#### **BMJ** Open

0.8. Additionally, to account for factors such as patient mortality and loss to follow-up in the ICU, and considering a 20% dropout rate, this study intends to recruit a total of 324 participants, with 162 participants in each group.

#### **Randomisation and allocation concealment**

We utilised a paired randomization method to match eligible participants based on a validated delirium risk scoring model for ICU patients. The scores ranged from 0 to 1, and patients with similar risk scores were paired. For example, Patient A, a 62-year-old male with an APACHE-II score of 14, had a risk score of 0.33, while Patient B, a 56-year-old male with an APACHE-II score of 16, had a risk score of 0.32. Therefore, Patients A and B exhibited similar scores. Next, random numbers were generated using the randomisation.com website, and based on these generated random numbers, the paired subjects were randomly allocated to either the intervention group or the control group. Concealed allocation, achieved through using consecutively numbered, sealed and opaque envelopes, will be performed by a research assistant with no further involvement in the research after participant enrollment.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES).

Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

### Blinding

Owing to the nature of the intervention, the researchers responsible for delivering the intervention will be aware of the group assignment. However, the outcome assessors will remain blinded to the group allocation and will not participate in data analysis or result reporting.

#### Intervention

Participants allocated to the intervention group will receive a VR-based sensory stimulation intervention plus usual care. This intervention is designed to provide VR-based visual and auditory stimulation to ICU patients, with additional support from family caregivers. The intervention will be administered by researchers who are trained ICU nurses. It will commence upon the patient's admission and continue until the fourteenth day of their ICU hospitalization or

the day of discharge if their stay is less than 14 days. Each day, a 30-minute session will be conducted (23–25).

The investigator will provide a delirium knowledge leaflet and a sample reorientation message to family caregivers in the intervention group. The investigator will spend 30 minutes explaining the contents to family caregivers during their first meeting. Family caregivers will be asked to prepare the family photographs, family video or recording at their earliest convenience. The leaflet contains information about the definition, prevalence and risk factors of delirium, along with practical steps family caregivers can take to support the patients. These steps include engaging in simple conversations, reminding patients of the current time, date, and location, providing glasses or hearing aids when necessary, decorating patient beds with family photographs, and discussing familiar topics. The reorientation messages serve to help patients understand their surroundings and offer encouragement. Each segment of the message requires two minutes for recording, following the sample message. The leaflet was designed by the investigator, and the sample reorientation message was adapted from a previous study(25). Both the leaflet and the sample orientation message were reviewed by a committee comprising three ICU nurse specialists, two nurse academics, one physician and two family caregivers.

Each daily session will commence at the earliest available daytime hour, typically between 12:00 and 16:00, following the completion of family recordings. During the pre-bedside phase, the investigator will gather family photographs, recordings, and videos, either digitally recorded or retrieved from previous family collections stored on electronic devices. Subsequently, the investigator will spend 30 minutes with each patient in the intervention group, tailoring the intervention based on the patient's ability to engage with auditory or visual stimulation (Figure 2). Notably, the intervention will be discontinued for trial participants under conditions such as participant requests or fluctuations in disease status.

#### **BMJ** Open

Implementation Content: The intervention consists of the following stages: (1) Guidance Stage (2 minutes): Introducing the content and purpose of the VR scenes to be played in the next 30 minutes; 2 Relaxation Stage (5 minutes): Selecting natural scenery VR scenes accompanied by soothing background music to help patients relax; ③ Family and Friends Support Stage (18) minutes): Playing VR scene videos provided by family and friends, selecting happy moments and conveying family wishes and blessings; ④ Feedback Stage (5 minutes): Guiding patients to provide feedback and collecting relevant parameters, such as heart rate, respiration, pain, etc.

## **Control group**

Participants in the control group will receive the usual care, consistent with their existing or planned treatment routines. Registered ICU nurses will administer the same nursing care, which includes, but is not limited to, sedation, analgesia, spontaneous breathing trials, indwelling catheter management, feeding, and bowel care.

### **Outcome and outcome measures**

The research will measure the following outcomes. See **Table 1**.

	Data Collection Time Points							Endpoint
Outcome Measures	Day1	Day2	Day3				Day14 / Discha rge	6 Months Post- Discharge
Delirium Score (CAM-ICU)	Х	Х	Х				X	
Sedation Score (RASS)	Х	Х	Х				X	
Pain Score (NRS)	Х	Х	Х				X	
Pain Score (BPAT) Sleep (RCSQ)	Х	Х	Х				X	
				9				

# Table 1 Outcomes and time schedules for data collection

Protected by copyright, including for uses related to text and

Page	10	of	28
------	----	----	----

	Х	Х	Х	 	 Х	
Post-traumatic stress disorder (PCL)					X	
ICU Memory (ICUMT)					X	
Patient Clinical Outcomes					X	
Ouality of Life Score						
(EuroQol)	Х				X	Х
Independence Function					•	
(motor-FIM)	Х				Х	Х
Cognitive function					•	
(cognitive-FIM)	Х				Х	Х

Note: CAM-ICU, Confusion Assessment Methods for Intensive Care Units; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPAT, behavior pain assessment tool; RCSQ, Richards-Campbell Sleep Questionnaire; PCL, Posttraumatic Stress Disorder Checklist; ICUMT, Intensive Care Unit Memory Tool; EuroQol, European Health Index; FIM, Functional Independence Measure;

## **Primary outcomes**

### Delirium incidence and duration

Delirium incidence means the number of patients who are delirious, which will be measured using the Confusion Assessment Methods for the Intensive Care Units (CAM-ICU) flow sheet. The CAM-ICU is comprised of four features, namely fluctuation of mental status, inattention, altered level of consciousness, and disorganised thinking. CAM-ICU was commonly adopted in ICU settings to measure delirium and was reported to have good interrater reliability (overall kappa coefficient = 0.71)(26).

## Delirium duration

The delirium duration will be calculated when the patient is first considered to have delirium to the last time that patient is not supposed to have delirium based on CAM-ICU. The delirium will be measured every eight hours during patients' stay using CAM-ICU.

Delirium Severity

#### **BMJ** Open

CAM-ICU-7 Delirium Severity Scale is a 7-point rating scale derived from the CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments. The final CAM-ICU-7 score ranges from 0-7 with 7 being most severe. CAM-ICU-7 scores are further categorised as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium. CAM-ICU-7 showed a high internal consistency (Cronbach's a = 0.85) and good correlation with Delirium Rating Scale-Revised - 98 (DRS-R-98) (correlation coefficient = 0.64)(27).

## Secondary outcomes

#### RCSQ

The Richards-Campbell Sleep Questionnaire (RCSQ) is employed to assess the sleep quality of ICU patients. Originally developed for evaluating sleep in critically ill patients, this questionnaire is designed to capture various aspects of sleep during the ICU stay. The scale evaluates perceptions of sleep depth, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality. The content validity of the Chinese version of the RCSQ questionnaire is 0.840, and the Cronbach's  $\alpha$  coefficient is 0.874.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

#### PTSD

The 17-item PTSD Checklist (PCL) correspond to the DSM-III-R symptoms of PTSD and serves as a self-report scale for assessing PTSD(28,29). Patients will be asked to rate their agreement with each item on a scale from one (not at all) to five (extremely). PTSD-symptoms are categorized into re-experiencing (flashback, nightmare, emotional cue reactivity, and physical cue reactivity), avoidance and emotional numbing (avoidance of thoughts and reminders, amnesia, loss of interest, detachment, restricted affect, and foreshortened future), and hyperarousal (irritability/anger, sleep disturbance, difficulty concentrating, hypervigilance, exaggerated startle response). The total score ranges from 17 to 85(30).

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) .

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

A previous study confirmed the good reliability and validity of the PCL, including testretest reliability of 0.96, internal consistency reliability of 0.94, and predictive validity of 0.64(31). High correlations with the Symptom Checklist-90 further confirm its reliability and validity(32).

#### ICU memory

The ICU-Memory Tool (ICU-M) will be used to measure ICU patients' ICU experience(33). This tool includes 14 questions (five open-ended questions and nine closed-ended questions), and is primarily divided into three parts: memories before admission to the ICU; memories during the ICU stay and memories after transferring out of the ICU. Memories during the ICU stay are categorized into three subscales: factual memories (lights, alarms, voices, families, faces, breathing tube, suctioning, darkness, clock, tube in your mouth, and wound care), memories of feelings (discomfort, confusion, sadness, anxiety/fear, panic, and pain), and memories of delusions (feeling that people were trying to hurt you, hallucinations, nightmares, dreams). The total number of memories in each of the three subscales will be summed. The Chinese version of ICU-M has a Cronbach's  $\alpha$  coefficient of 0.823 and a scale-level content validity index of 0.946, confirming its good reliability and validity(34).

### Patients' clinical outcomes

Medical outcomes will be extracted by the outcome assessor from the electronic health care system upon participants' discharge. This information includes: (a) ICU length of stay: the total number of days a patient stays in ICU; (b) 30-day mortality: the total death cases among all eligible cases at 30 days after admission to ICU; (c) duration of mechanical ventilation: the registered time in hours that the patients are on the mechanical ventilator; (d) the duration of use of physical restraint: the recorded time in hours that the patients are receiving physical restraint;

(e) sedation use: the documented total amount and average doses (mg/ per day) of sedation by using the conversion measurement of the same quantity of dexmedetomidine. (f) analgesics use: the documented total amount and average doses (mg/ per day) of analgesics using the conversion measurement of the same quantity of propofol. (g) self-extubation: the documented amount of self-extubation cases; (h) ICU acquired infection: the documented amount of self-acquired infection cases.

Quality of life

The EuroQol- 5 Dimension (EQ-5D) will be used to assess the participants' quality of life. It assigns a grade on a scale ranging from 0 (representing the worst possible health status) to 100 (representing the best possible health status) based on one question for each of the five dimensions, including mobility, self-care, usual activities, pain/discomfort, and

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

anxiety/depression(35).

Independence and cognitive function

FIM (Functional Independence Measure) will be used to measure both the independence and cognitive function. The FIM is comprised of 18 items, which are grouped into two subscales: motor and cognition. The motor items are adapted from the Barthel Index and are collectively known as the Motor-FIM. These items includes: Eating, Grooming, Bathing, Dressing (upper body), Dressing (lower body), Toileting, Bladder management, Bowel management, Transfers (bed/chair/wheelchair), Transfers (toilet), Transfers (bath/shower), Walk/wheelchair, and Stairs. The cognition subscale, known as the Cognitive-FIM, includes the following items: Comprehension, Expression, Social interaction, Problem solving, and Memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 to 7. A higher score indicates greater independence in performing the task associated with that item. The

Inter-Rater Reliability of FIM has been established with acceptable psychometric performance,

with Intraclass corelation coefficients ranging from 0.86 to 0.88. Concurrent validity with the

Barthel Index (ICC > 0.83) have demonstrated strong construct validity between items on

Barthel Index and items on the FIM the measure functional limitations (36).

# Sociodemographic and clinical information

Sociodemographic and clinical information including ICU patients and family caregivers' age, gender, educational level, marital status, occupation, the relationship between ICU patients and family caregivers, and the health history of ICU patients will be collected.

Session	Content	Content Description
Pre-	Clarify Team	Define roles for team members including software requirements, software testing,
Implementation	Member Roles	case selection, recruitment, intervention training, intervention implementation,
		outcome assessment, data management, statistics, and supervision personnel.
	Organize	Provide standardised training for intervention personnel to ensure consistency in
	Research	the intervention program.
	Member	
	Training	
	Prepare	Develop intervention implementation guidelines, flowcharts, intervention logs, and
	Materials	intervention checklists.
Implementation	Detailed	Record the implementation process and any omissions using intervention logs.
	Recording	
	Supervision	Conduct process audits of the intervention by a nurse manager not involved in the
	Auditing	research.
	Regular	Provide regular project progress reports, assess the evaluation, and make necessary
	Reporting	research adjustments.
	Fidelity	Assess the adherence to intervention elements, dosage, and protocols.
Post-	Standardized	Double-check and enter follow-up questionnaires.
Implementation	Information	
	Management	
	Identify and	Correct errors by manually checking the original dataset, using box plots,
	Correct Errors	histograms, and scatter plots, and using descriptive statistics.
		14
		14

# Table 2 Content of process evaluation and intervention integrity

Page 15 of 28

Session	Content	Content Description
	Handling	Supplement missing data through participant contact and medical record queries.
	Missing Data	
	Analyze	Compare observed and unobserved statistical differences.
	Statistic	
	Differences	
	Use Intention-	Perform analysis using the intention-to-treat approach.
	to-Treat (ITT)	
	Analysis	

## **Data collection**

The principal investigator will begin by explaining the study and obtaining written informed consent from the participants. Afterward, a research assistant, who is a postgraduate student majoring in nursing, will proceed to retrieve patients' demographic data from their medical records and collect information on their quality of life, independence, and cognitive function prior to admission to the ICU from the participants' family caregivers. The nurses in charge of the study ICU will assess the CAM-ICU, RASS, RCSQ during daily routine. On the fourteenth day of a patient's ICU hospitalization, or upon discharge if the ICU stay is less than 14 days, the research assistant will collect data on secondary measures (PTSD, ICU memory), clinical outcomes, independence, and cognitive function. Additionally, quality of life, independence, and cognitive function of the intervention.

### Data management

To identify and rectify errors, such as missing values, outliers, and typos, data cleaning strategies will be employed(37). Several methods will be employed to detect errors and minimise the impacts on the accuracy of results. Firstly, the original dataset (in Excel) will be manually checked to identify data error. Secondly, statistical graphical explorations including box plots,

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

histograms and scatter plots, along with descriptive statistics such as mean, frequency, and percentage, will be used. Through this process, data errors, including typos, outliers, and violations of integrity constraints, will be corrected.

#### Data analysis

This study will use SPSS 25.0 and R 23.0 software for data analysis. All statistical tests will be two-tailed, with the significance level set at 0.05. To assess the normal distribution of continuous variables, skewness, kurtosis, Q-Q plots, and histograms will be examined. Variables with skewness and kurtosis values within the range of -2.0 to 2.0 will be considered to have a normal distribution. For normally distributed continuous variables, the study will describe them using the mean  $\pm$  standard deviation (Mean  $\pm$  SD). For variables that do not meet the normal distribution criteria, the study will describe them using the median (interguartile range, IOR). Categorical variables will be described using frequency (proportion). If the assumptions for hypothesis testing of continuous variables are met, paired-sample t-tests will be used to compare differences between different groups. Otherwise, the paired Wilcoxon signed-rank test will be employed. For categorical variables, Kappa consistency tests and paired chi-square tests (McNemar's test) will be used to compare differences between different groups. Additionally, missing values will be imputed using multiple imputation methods. The study will follow the intention-to-treat (ITT) principle for analysis. After imputing missing data using multiple imputation methods, the study will perform ITT analysis and report relevant

uncertainty indicators, such as confidence intervals and standard errors, in the results.

Furthermore, this study will use mixed-effects models to analyze differences between groups in delirium duration, delirium severity, psychological outcomes, and other outcomes.

#### BMJ Open

## DISCUSSION

This study aims to evaluate the effects of a VR-based sensory stimulation on preventing delirium and improving various patient outcomes, including psychological measures (sleep quality, post-traumatic stress disorder, ICU memory), clinical outcomes (ICU length of stay), and other measures (quality of life, independence, and cognitive function).

The research team will follow the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. Ethical approval has been obtained from the Ethics Committee of the study hospital. Written consent will be acquired from eligible participants or their surrogates. All collected data will be kept strictly confidential and used exclusively for the purposes of this study. The research report will not contain any personal information of the participants.

The study has been registered in the Centre for Clinical Research and Biostatistics after obtaining ethical approval and before the recruitment of participants. Results of this RCT study will be disseminated via peer-reviewed journals and presentations at local, national and international conferences. BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) .

data mining, Al training, and similar technologies

Protected by copyright, including for uses related to text and

### **Funding statement**

This study has received support from the China Postdoctoral Science Foundation (2023M731551) and the Science and Technology Project of Shenzhen (JCYJ20230807142300002).

## **Competing interests statement**

The authors declare that they have no competing interests.

## **Patient and Public Involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Word counts: 3453

Figure 1: Diagram of the flow of the study

Figure 2: Flowchart of VR-based sensory stimulation implementation

# References

 Jayaswal AK, Sampath H, Soohinda G, Dutta S. Delirium in medical intensive care units: Incidence, subtypes, risk factors, and outcome. Indian J Psychiatry. 2019;61(4):352– 8.

2. Gravante F, Giannarelli D, Pucci A, Gagliardi AM, Mitello L, Montagna A, et al. Prevalence and risk factors of delirium in the intensive care unit: An observational study. Nurs Crit Care. 2021 May;26(3):156–65.

3. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FEJ, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr;291(14):1753–62.

4. Liang S, Chau JPC, Lo SHS, Bai L, Yao L, Choi KC. Validation of PREdiction of DELIRium in ICu patients (PRE-DELIRIC) among patients in intensive care units: A retrospective cohort study. Nursing in Critical Care. 2021 May;26(3):176–82.

Mehta S, Cook D, Devlin JW, Skrobik Y, Meade M, Fergusson D, et al.
 Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. Crit Care
 Med. 2015 Mar;43(3):557–66.

 Wolters AE, Peelen LM, Welling MC, Kok L, de Lange DW, Cremer OL, et al. Long-Term Mental Health Problems After Delirium in the ICU. Crit Care Med. 2016 Oct;44(10):1808–13.

7. Liang S, Chau JPC, Lo SHS, Zhao J, Choi KC. Effects of nonpharmacological delirium-prevention interventions on critically ill patients' clinical, psychological, and family

#### **BMJ** Open

outcomes: A systematic review and meta-analysis. Australian Critical Care. 2021 Jul;34(4):378– 87.

8. Liang S, Chau JPC, Lo SHS, Choi KC, Bai L, Cai W. The effects of a sensory stimulation intervention for preventing delirium in a surgical intensive care unit: A randomized controlled trial. Nursing in Critical Care. 2023 Sep;28(5):709–17.

9. Liang S, Pak Chun Chau J, Hoi Shan Lo S, Chow Choi K, Bai L, Cai W. The effects of a sensory stimulation intervention on psychosocial and clinical outcomes of critically ill patients and their families: A randomised controlled trial. Intensive and Critical Care Nursing. 2023 Apr;75:103369.

10. Strøm BS, Ytrehus S, Grov EK. Sensory stimulation for persons with dementia: a review of the literature. J Clin Nurs. 2016 Jul;25(13–14):1805–34.

11. Moattari M, Alizadeh Shirazi F, Sharifi N, Zareh N. Effects of a Sensory Stimulation by Nurses and Families on Level of Cognitive Function, and Basic Cognitive Sensory Recovery of Comatose Patients With Severe Traumatic Brain Injury: A Randomized Control Trial. Trauma Mon. 2016 Sep;21(4):e23531.

12. Liang S, Chau JPC, Lo SHS, Zhao J, Liu W. Non-pharmacological delirium prevention practices among critical care nurses: a qualitative study. BMC Nurs. 2022 Aug 25;21(1):235.

 Liang S, Chau JPC, Lo SHS, Li S, Gao M. Implementation of ABCDEF care bundle in intensive care units: A cross-sectional survey. Nursing in Critical Care. 2021 Sep;26(5):386–96.

14. Luan L, Ding M. Progress in the application of virtual reality technology in critically ill patients in ICU. Chinese Journal of Nursing. 2021 Aug 15;56(8):1255.

15. Jawed YT, Golovyan D, Lopez D, Khan SH, Wang S, Freund C, et al. Feasibility of a virtual reality intervention in the intensive care unit. Heart Lung. 2021;50(6):748–53.

Page 20 of 28

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

#### **BMJ** Open

> 16. Ong TL. The DREAMS Project: Improving the Intensive Care Patient Experience with Virtual Reality [Internet]. [cited 2023 Oct 13]. Available from: https://arxiv.org/abs/1906.11706

17. Ong TL, Ruppert MM, Akbar M, Rashidi P, Ozrazgat-Baslanti T, Bihorac A, et al. Improving the Intensive Care Patient Experience With Virtual Reality-A Feasibility Study. Crit Care Explor. 2020 Jun;2(6):e0122.

18. Restorative effects of virtual nature settings - PubMed [Internet]. [cited 2023 Oct
13]. Available from: https://pubmed.ncbi.nlm.nih.gov/20950174/

19. Ohly H, White MP, Wheeler BW, Bethel A, Ukoumunne OC, Nikolaou V, et al. Attention Restoration Theory: A systematic review of the attention restoration potential of exposure to natural environments. J Toxicol Environ Health B Crit Rev. 2016;19(7):305–43.

20. Chirico A, Cipresso P, Yaden DB, Biassoni F, Riva G, Gaggioli A. Effectiveness of Immersive Videos in Inducing Awe: An Experimental Study. Sci Rep. 2017 Apr 27;7(1):1218.

21. Toyabe S ichi, Kouhei A. Referral from secondary care and to aftercare in a tertiary care university hospital in Japan. BMC Health Services Research. 2006;6(1):11.

22. Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003 Jun;289(22):2983–91.

Moon K, Lee S. The effects of a tailored intensive care unit delirium prevention protocol: A randomized controlled trial. International journal of nursing studies.
 2015;52(9):1423–32.

24. Mailhot T, Cossette S, Côté J, Bourbonnais A, Côté MC, Lamarche Y, et al. A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study. Nursing in critical care. 2017 Jul;22(4):221–8.

#### **BMJ** Open

25. Munro C, Cairns P, Ji M, Calero K, Anderson W, Liang Z. Delirium prevention in critically ill adults through an automated reorientation intervention – A pilot randomized controlled trial. Heart & Lung - The Journal of Acute and Critical Care. 2017;46(4):234–8.

26. Zou J. Reliability and validity test of Chinese version of CAM-ICU and comparison with other scales. Huazhong University of Science and Technology; 2012.

27. Babar A. Khan, Perkins Anthony J, Sujuan Gao, Siu L. Hui, Campbell L. Noll, Farber Mark O, Chlan Linda L BMA, Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, et al. The CAM-ICU-7 Delirium Severity Scale: A novel delirium severity instrument for use in the Intensive Care Unit. Critical care medicine. 2017;45(5):851–7.

28. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility. New York: Guilford Press; 1993.

29. Mollica RF, Caspi-yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard trauma questionnaire: Validating a cross-cultural instrument for measuring torture, trauma, and posttraumatic stress disorder in indochinese refugees. The journal of nervous and mental disease. 1992;180(2):111–6.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

30. Svenningsen H, Egerod I, Christensen D, Tonnesen EK, Frydenberg M, Videbech
P. Symptoms of posttraumatic stress after intensive care delirium. BioMed Research
International. 2015;

31. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD checklist (PCL). Behaviour research and therapy. 1996;34(8):669–73.

32. Yang L, Yang X, Yang H, Liu Q. Study on the validity, reliability and influencing factors of the civilian version of the Post-traumatic Stress Checklist. Chinese Journal of Health Psychology. 2007;15(1):6–9.

Jones C, Humphris G, Griffiths RD. Preliminary validation of the ICUM tool: a tool for assessing memory of the intensive care experience. Clinical Intensive Care.
 2000;11(5):251–5.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

ta mining, Al training, and similar technologies

Protected by copyright, including for uses related to text and

34. Huang L, Jiang Q, Lin X, Hou W, Wang S, Wang X. The reliability and validity test of ICU Memory Scale. Chinese Journal of Nursing. 2016;51(10):1265–9.

35. Balestroni G, Bertolotti G. [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. Monaldi Arch Chest Dis. 2012 Sep;78(3):155–9.

36. Parallel reliability of the functional independence measure and the Barthel ADL index - PubMed [Internet]. [cited 2023 Oct 13]. Available from:

https://pubmed.ncbi.nlm.nih.gov/11117590/

37. Van Den Broeck J, Cunningham SA, Eeckels R, Herbst K. Data cleaning: Detecting, diagnosing, and editing data abnormalities. PLoS medicine. 2005;2(10):966–70.





1	
3	
4	Title page
5 6	Title: Effectiveness of a Virtual Reality-based sensory stimulation intervention on
7 8 9	preventing delirium in Intensive Care Units: a randomised controlled trial protocol
10	
11 12	Authors: Surui Liang <sup>1</sup> , PhD; Jinfei Tian <sup>2</sup> , MM; Yong Liu <sup>2</sup> , PhD; Taoxue Wen <sup>2</sup> , MM;
13 14	Dan Luo <sup>2</sup> , MM; Wenzhi Cai <sup>1*</sup> , PhD.
15 16	Address 1: Department of Nursing, Shenzhen Hospital, Southern Medical University,
17	Shenzhen, Guangdong, China
19	Address 2: Department of Intensive Care Unit, Shenzhen Hospital, Southern Medical
20	University, Shenzhen, Guangdong, China
22 23	*: Corresponding author
24 25	
26 27	Surui Liang liangsurui@link.cuhk.edu.hk
28 29	Linfei Tian 18907287566@163.com
30	Vang Liv live give govelock com
32	
33 34	$1 \text{ aoxue Wen } \underline{\text{wentx} 2000(a) 126.com}$
35	Dan Luo <u>2274060957@qq.com</u>
36 37	Wenzhi Cai <u>caiwzh@smu.edu.cn</u>
38	Corresponding author: Wenzhi Cai
39	
40	Address: Department of Nursing, Shenzhen Hospital, Southern Medical University,
42 43	Shenzhen, Guangdong,China
44	Telephone: (86) 18002575566 Email: caiwzh@smu.edu.cn
45 46	
47	
48	Contributors LSR, TJF, LD designed the study and wrote manuscript. CWZ, WTX
49 50	and LY are members of the study team who contributed to the development of the
51	study methods. All authors approved the final version of the manuscript
5∠ 53	study methods. An authors approved the final version of the manuscript
54	First the This state has been associated associated for the Children Devil (1997)
55 56	running This study has received support from the China Postdoctoral Science
57	Foundation (2023M731551) and the Science and Technology Project of Shenzhen

(JCYJ20230807142300002).

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Competing interests None declared.

Patient consent for publication Not required.

**Ethics approval** This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068).

Trial registration number ClinicalTrials.gov NCT06153472. Trial registration date:

November 22, 2023



Page 28 of 28







359x288mm (72 x 72 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# **BMJ Open**

# Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-083966.R1
Article Type:	Protocol
Date Submitted by the Author:	04-May-2024
Complete List of Authors:	Liang, Surui; Shenzhen Hospital of Southern Medical University, Intensive Care Unit Liu, Yong; Shenzhen Hospital of Southern Medical University, Intensive Care Unit Wen, Taoxue; Shenzhen Hospital of Southern Medical University, Intensive Care Unit Luo, Dan; Shenzhen Hospital of Southern Medical University, Intensive Care Unit He, Mingxin; Peking University Shenzhen Hospital, Intensive Care Unit Tian, Jinfei; Shenzhen Hospital of Southern Medical University, Intensive Care Unit
<b>Primary Subject Heading</b> :	Nursing
Secondary Subject Heading:	Neurology
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, INTENSIVE & CRITICAL CARE, Virtual Reality

SCHOLARONE<sup>™</sup> Manuscripts

1		
2 3 4	1	Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing
5 6	2	Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol
/ 8 9	3	Authors. Surui Liang <sup>1*</sup> , PhD; Yong Liu <sup>1</sup> , PhD; Taoxue Wen <sup>1</sup> , MM; Dan Luo <sup>1</sup> , MM; Xinming
10 11	4	He <sup>2</sup> , MM; Jinfei Tian <sup>1</sup> , MM.
12 13	5	Address 1: Department of Intensive Care Unit, Shenzhen Hospital of Southern Medical
14 15 16	6	University, Shenzhen, Guangdong,China
17 18	7	Address 2. Department of Intensive Care Unit, Peking University Shenzhen Hospital,
19 20	8	Shenzhen, Guangdong,China
21 22 23	9	*: Corresponding author
24 25	10	Surui Liang liangsurui@link.cuhk.edu.hk/liangsr5@mail2.sysu.edu.cn
26 27	11	Yong Liu liuyongjoy@outlook.com
28 29	12	Taoxue Wen wentx_2000@126.com
30 31 32	13	Dan Luo luodan0325@hotmail.com
33 34	14	Mingxin He_xiaoming695318082@outlook.com
35 36 37	15	Jinfei Tian 18907287566@163.com
37 38 39	16	Corresponding author: Surui Liang
40 41	17	Address: Department of Intensive Care Unit, Shenzhen Hospital, Southern Medical
42 43	18	University, Shenzhen, Guangdong, China
44 45 46	19	Telephone: (86) 17801305403 Email: liangsr5@mail2.sysu.edu.cn
47 48	20	Contributors SL, YL, DL, FT designed the study and wrote the manuscript. SL is the
49 50	21	principal investigator and data management leader. MH, TW, and YL are members of the
51 52	22	study team who contributed to the development of the study methods, and team members
52 53 54	23	supervised the trial. All authors approved the final version of the manuscript.
55 56	24	Funding This study has received support from the China Postdoctoral Science Foundation
57 58	25	(2023M731551) and the Science and Technology Project of Shenzhen
59 60	26	(JCYJ20230807142300002).

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

**BMJ** Open

1	Competing interests None declared.
2	Patient consent for publication Not required.
3	Ethics approval This protocol was approved by Research Ethics Committee of Shenzhen
4	Hospital of Southern Medical University (NYSZYYEC20230068).
5	Trial registration number Clinical Trials.gov NCT06153472. Trial registration date.
6	November 22, 2023
7	Version of the trial protocol, date, and version identifier: 2023K089; Verification Date: April
8	2024; version identifier: Version 1.
9	This study has received support from the China Postdoctoral Science Foundation
10	(2023M731551) and the Science and Technology Project of Shenzhen
11	(JCYJ20230807142300002). No intervention is conducted by the sponsors in the research
12	design, data collection, management, analysis and interpretation of data, report writing,
13	publication, etc.
14	
15	

**BMJ** Open

2 3	1	
4 5	1	
6	2	ABSTRACT
/ 8	3	Introduction:
9 10 11	4	Delirium is a common acute cognitive impairment characterized by confusion, disorientation,
12 13	5	and attention deficits, particularly prevalent in ICU settings. Given its significant impact on
14 15	6	patients, caregivers, and healthcare resources, preventing delirium in ICU patients is of
16 17	7	paramount importance. This is the first randomized controlled trial (RCT) designed to
18 19 20	8	evaluate the effects of a Virtual Reality-based sensory stimulation intervention on preventing
21 22	9	delirium in intensive care unit (ICU) patients.
23 24	10	Methods and Analysis:
25 26 27	11	We employed a paired randomization method to match eligible participants based on a
27 28 29	12	validated delirium risk scoring model for ICU patients. The study will commence in
30 31	13	September 2024 and conclude in June 2026. A consecutive sample of 324 ICU patients
32 33	14	admitted to the study setting will be recruited. Eligible participants will be randomly
34 35 36	15	allocated to receive either Virtual Reality-based sensory stimulation in addition to usual care
37 38	16	or usual care alone. The Virtual Reality-based sensory stimulation intervention will last for
39 40	17	up to fourteen days, with all interventions administered by a research team. We define
41 42 43	18	delirium-free days over a 14-day period as the primary outcome. The secondary outcomes
44 45	19	will include delirium incidence, duration, and severity, patients' psychological well-being
46 47	20	(post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes,
48 49 50	21	and other outcomes (quality of life, independence, and cognitive function). Data will be
50 51 52	22	collected at baseline, post-intervention, and six months post-intervention. Two independent t-
53 54	23	tests or Wilcoxon-Mann-Whitney tests will be utilized for continuous variables, while chi-
55 56 57 58 59	24	square or Fisher's exact tests will be employed for categorical variables. The analysis will

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

adhere to both the intention-to-treat and per protocol principles. Additionally, mixed-effects models and subgroup analysis will be planned. **Ethics and dissemination** This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068). All participants or their family caregivers will provide written informed consent. Results will be disseminated through scientific publications, and presentations at local and international conferences. Trial registration number ClinicalTrials.gov NCT06153472. Trial registration date: November 22, 2023 Word counts: 232 Keywords: Critical care; Delirium, Virtual Reality, Sensory stimulation **Article Summary** Strengths and limitations of this study ► This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function). ► This study utilizes a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention for preventing delirium in ICUs. The methodological rigor of this design enhances the reliability and validity of our findings, providing valuable insights into the effectiveness of such interventions in clinical settings. ▶ Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible. 

#### BMJ Open

3	
4	
5	
6	
7	
, Q	
0	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
20 21	
∠ I วว	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
27	
J∠ 22	
22	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
16	
40	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
50	

1	INTRODUCTION
2	Delirium is a common acute state of cognitive confusion. Intensive Care Unit (ICU)
3	delirium is highly prevalent, with an incidence ranging from 31%(1) to 56%(2), and it can be as
4	high as 81%(3) in ICU patients undergoing mechanical ventilation. A preliminary analysis of
5	data from 375 patients admitted to the ICU for more than 24 hours revealed an occurrence rate of
6	44% for ICU delirium(4). Moreover, delirious ICU patients had 1.33 times longer ICU stays and
7	a 9.57-fold increase in mortality compared to non-delirious ICU patients(5). ICU patients who
8	experience delirium may suffer from post-traumatic stress disorder, anxiety, depression, and
9	cognitive impairment for up to two years(6).
10	Non-pharmacological preventive measures aim to reduce one or more modifiable risk
11	factors for ICU delirium(7). Previous research identified sensory stimulation as a key and
12	effective non-pharmacological intervention in preventing ICU delirium(8,9). Sensory stimulation
13	involves activating one or more senses(10), with visual and auditory stimuli being particularly
14	effective for ICU patients(11). To further investigate the effectiveness of sensory stimulation in
15	preventing ICU delirium, the research team conducted an initial study to assess the
16	implementation of sensory stimulation on preventing delirium in ICU and subsequently
17	developed a sensory stimulation intervention plan(12,13). This plan involved daily sessions of 30
18	minutes each for seven days, including visual stimuli (displaying personal or family photos) and
19	auditory stimuli (playing recordings of family members). The results of the study showed that
20	sensory stimulation reduced the duration and severity of ICU delirium but did not significantly
21	decrease the incidence of ICU delirium(8,9). The limited effectiveness of sensory stimulation
22	may be attributed to the narrow range of stimuli, insufficient stimulus intensity, and inadequate
23	dosing and implementation methods(9).
BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
20	
27	
28	
29	
20 21	
ו כ ככ	
⊃∠ ככ	
27	
25	
36	
30	
38	
30	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

1	In contrast, Virtual Reality (VR) technology, characterized by its three-dimensional and
2	highly immersive qualities, has the potential to provide more effective sensory stimulation by
3	immersing participants in three-dimensional dynamic environments(14). International research
4	suggests that VR offers significant advantages in sensory stimulation and could be a promising
5	approach for preventing ICU delirium, however, it's important to note that studies on the use of
6	VR in preventing ICU delirium are currently in the feasibility testing stage(15–17). The
7	DREAMS project at the University of Florida in the United States investigated the effectiveness
8	of VR and found that 95.6% of participants found it very comfortable, 51.9% reported improved
9	sleep quality, and 81.5% experienced reduced pain(16). This team further conducted a study with
10	46 ICU patients, implementing a seven-day VR intervention, which resulted in reduced stress,
11	pain, anxiety, and improved cognitive function and attention in the participants(17).
12	Additionally, Jawed and colleagues conducted a preliminary trial that showed VR could alleviate
13	anxiety in ICU patients(15). However, since those studies were in the feasibility testing stage,
14	they were unable to measure the effects on reducing ICU delirium.
15	The stress recovery theory and attention restoration theory explain the principles behind
16	preventing ICU delirium using VR-based sensory stimulation(18,19). The stress recovery theory
17	suggests that natural environments support positive changes in emotional states and
18	psychophysiological recovery, primarily by relaxing the parasympathetic nervous system (19).
19	In stressful ICU environments, cognitive and attentional resources can become fatigued, which is
20	especially crucial for critically ill patients facing stressors. The cognitive demands and
21	overstimulation in the ICU environment contribute to mental fatigue and stress responses(19).
22	On the other hand, the attention restoration theory suggests that exposure to natural environments
23	requires fewer cognitive resources and promotes a sense of disengagement from stressors,

1	allowing attention to rest and recover(18). Therefore, VR-based visual and auditory stimuli, by
2	immersing patients in relaxing VR environments, may have a protective effect against
3	environmental stress and aid in the recovery of physiological, emotional, and attentional
4	functions, thus preventing delirium. Chirico and colleagues further elucidated the mechanisms of
5	VR-based sensory stimulation in delirium prevention: exposure to VR-based natural
6	environments can trigger a specific psychophysiological pattern activated by the parasympathetic
7	nervous system, leading to intense emotional reactions(20). Emotion responses increase with
8	higher levels of immersion, which can be utilized to alleviate symptoms like anxiety, pain, and
9	fear, effectively reducing patient stress, improving sleep quality, and consequently reducing the
10	incidence of delirium(20).
11	Aim and hypothesis
12	This study aims to evaluate the effects of evaluates a Virtual Reality-based sensory stimulation
13	on preventing delirium, and improving patients' psychological (post-traumatic stress disorder,
14	sleep quality, ICU memory), patients' clinical (ICU length of stay) and other outcomes (quality
15	of life, independence and cognitive function). And the comparator in our study is 'usual care,'
16	representing the standard treatment or practices typically provided in similar clinical settings.
17	It is hypothesised that at patients' fourteenth day of ICU hospitalisation or the day of discharge
18	(if the ICU stay is less than 14 days), will experience the following improvements compared with
19	those receiving usual care.
20	1. ICU patients receiving the sensory stimulation intervention will have:
21	a. A reduction in incidence, duration and severity of delirium.
22	b. An improvement in their post-traumatic stress disorder.
23	c. An improvement of factual memories.
	7
	For peer review only - http://bmiopen.bmi.com/site/about/quidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1		
2		
5 Д	1	d. A shorter length of ICU stay.
5		
6	2	e. An improvement in quality of life, independence and cognitive function.
7		
8	3	At six months after completing the intervention, compared to those receiving usual care,
9		
10	4	ICU patients undergoing the VR-based sensory stimulation intervention will experience an
11		
12 12	5	improvement in quality of life, independence, and cognitive function.
14		
15	6	METHODS AND ANALYSIS
16		
17	7	Design
18		
19	8	A multi-center assessor-blinded two-arm parallel group RCT will be conducted. Figure 1 shows
20		
21 22	9	the study flow.
22	-	
24	10	Setting
25	10	
26	11	Participants will be recruited from general ICUs of Shenzhen Hospital of Southern Medical
27	11	
28	12	University and Shenzhen Hospital of Beijing University, two comprehensive tertiary A -level
29	12	Oniversity and Shenzhen Hospital of Derjing Oniversity, two comprehensive tertiary AV level
30 21	12	hospitals in Shanzhan, Guangdong province, Mainland China, Tartiary A, lavel hospital provides
21 22	15	nospitals in Shenzhen, Guangdong province, Mannand China. Tertiary A-lever nospital provides
33	14	specialist tertiary ears in a large bespital after a referral from primary and secondary ears (21)
34	14	specialist tertiary care in a large hospital after a referrar from primary and secondary care.(21)
35	1.5	Doutisinants
36	15	Parucipants
37	16	All ICLI notion to a dmitted to the study setting will be near ited if they are they at (1) and 10 years
38	16	All ICO patients admitted to the study setting will be recruited if they are/nave: (1) aged 18 years
39 40	17	an alden (2) first time a devision to the ICIU and (2) a Dishmand Arithm Cadation Cash
40 41	17	or older, (2) first-time admission to the ICU, and (3) a Richmond Agitation-Sedation Scale
42	10	
43	18	(RASS) score of $\geq -3(22)$ . Patients will be excluded if they have: (1) been diagnosed with
44		
45	19	dementia, delirium or acute psychiatric illness at admission, (2) been diagnosed with end-stage
46		
47	20	cancer, (3) severe hearing impairment and cannot be corrected by hearing aids and (4) been
48		
49 50	21	admitted to ICU with radioactive material.
51		
52		
53		
54		
55		
56		

1
2
3
1
4 5
5
6
7
8
9
10
11
10
12
13
14
15
16
17
18
10
20
2U 21
21
22
23
24
25
26
20
27
28
29
30
31
32
33
34
25
22
36
37
38
39
40
41
12
ד∠ ⊿ר
43
44
45
46
47
48
49
50
50
51
52
53
54
55
56
57
57
20
59
60

1	Sample size determination
2	Sample size calculation for the difference test in delirium incidence between the
3	experimental and control groups was performed using G* Power 3.4. Based on a prior study,
4	delirium incidence after sensory stimulation was 13%, while it was 25% in the standard care
5	group, yielding an odds ratio of 0.57(8). For G* Power's two-sample proportion (z-test)
6	calculation, with a significance level set at $\alpha = 0.05$ and a desired test power of Power = 0.8,
7	the required sample size was determined to be 259 participants. Additionally, to account for
8	factors such as patient mortality and loss to follow-up in the ICU, and considering a 20% dropout
9	rate, this study intends to recruit a total of 324 participants, with 162 participants in each group.
10	Randomisation and allocation concealment
11	We employed a simple randomization method by generating random numbers through the
12	randomization.com website. Based on these generated numbers, participants were then randomly
13	assigned to either the intervention or control group. To ensure allocation concealment,
14	consecutively numbered, sealed, and opaque envelopes will be utilized. This process will be
15	conducted by a research assistant who will have no further involvement in the study after
16	participant enrollment.
17	Blinding
18	Owing to the nature of the intervention, the researchers responsible for delivering the
19	intervention will be aware of the group assignment. However, the outcome assessors will remain
20	blinded to the group allocation and will not participate in data analysis or result reporting.
21	Intervention
22	Participants allocated to the intervention group will receive a VR-based sensory stimulation
23	intervention plus usual care. This intervention is designed to provide VR-based visual and
	9

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

auditory stimulation to ICU patients, with additional support from family caregivers. The intervention will be administered by researchers who are trained ICU nurses. It will commence upon the patient's admission and continue until the fourteenth day of their ICU hospitalization or the day of discharge if their stay is less than 14 days. Each day, a 30-minute session will be conducted (23–25).

The investigator will provide a delirium knowledge leaflet and a sample reorientation message to family caregivers in the intervention group. The investigator will spend 30 minutes explaining the contents to family caregivers during their first meeting. Family caregivers will be asked to prepare the family photographs, family video or recording at their earliest convenience. The leaflet contains information about the definition, prevalence and risk factors of delirium, along with practical steps family caregivers can take to support the patients. These steps include engaging in simple conversations, reminding patients of the current time, date, and location, providing glasses or hearing aids when necessary, decorating patient beds with family photographs, and discussing familiar topics. The reorientation messages serve to help patients understand their surroundings and offer encouragement. Each segment of the message requires two minutes for recording, following the sample message. The leaflet was designed by the investigator, and the sample reorientation message was adapted from a previous study(25). Both the leaflet and the sample orientation message were reviewed by a committee comprising three ICU nurse specialists, two nurse academics, one physician and two family caregivers.

Each daily session will commence at the earliest available daytime hour, typically between 12:00 and 16:00, following the completion of family recordings. During the pre-bedside phase, the investigator will gather family photographs, recordings, and videos, either digitally recorded or retrieved from previous family collections stored on electronic devices. Subsequently, the investigator will spend 30 minutes with each patient in the intervention group,

Page 11 of 28

## BMJ Open

	Delirium Score (CAM-					
	Discha	Discharge				
	Outcome Measures Day14 Day1 Day2 Day3 Day14	6 Months Post-				
	Data Collection Time Points	Endpoint				
19	Table 1 Outcomes and time schedules for data collection	1				
18	The research will measure the following outcomes. See <b>Table 1</b> .					
17	Outcome and outcome measures					
16	catheter management, feeding, and bowel care.					
15	includes, but is not limited to, sedation, analgesia, spontaneous breathing trials, in	dwelling				
14	planned treatment routines. Registered ICU nurses will administer the same nursing	ng care, which				
13	Participants in the control group will receive the usual care, consistent with their e	existing or				
12	Control group					
11	provide feedback and collecting relevant parameters, such as heart rate, respiration	n, pain, etc.				
10	and conveying family wishes and blessings; ④ Feedback Stage (5 minutes): Gui	ding patients t				
9	minutes): Playing VR scene videos provided by family and friends, selecting happ	by moments				
8	by soothing background music to help patients relax; ③ Family and Friends Sup	port Stage (18				
7	30 minutes; ② Relaxation Stage (5 minutes): Selecting natural scenery VR scene	es accompanie				
6	Stage (2 minutes): Introducing the content and purpose of the VR scenes to be pla	yed in the nex				
5	Implementation Content: The intervention consists of the following stages	: ① Guidanc				
4						
3	conditions such as participant requests or fluctuations in disease status.					
2	stimulation (Figure 2). Notably, the intervention will be discontinued for trial part	icipants under				

ICU)	Х	Х	Х				Х	
Sedation Score (RASS)	Х	Х	Х				Х	
Pain Score (NRS)	Х	Х	Х				Х	
Pain Score (BPAT)	Х	Х	Х				Х	
Sleep (RCSQ)	x	x	x				x	
Post-traumatic stress disorder (PCL)							X	
ICU Memory (ICUMT)							Х	
Patient Clinical Outcomes							Х	
Quality of Life Score	v						v	v
Independence Function							Α	Λ
(motor-FIM) Cognitive function	Х						Х	Х
(cognitive-FIM)	X	<u>`</u>		<u> </u>	0 1		X	X
Note: CAM-ICU, Co	nfusioi	1 Asses	sment N	lethod	s for In	tensive (	Care Units; R	
Richmond Agitation-Sedatio	n Scale	e; NRS,	numeri	cal rati	ng scal	e; BPA I	l, behavior p	ain
assessment tool; RCSQ, Rich	nards-C	Campbe	ll Sleep	Questi	onnaire	e; PCL, I	Posttraumatio	c Stress
Disorder Checklist; ICUMT,	Intens	ive Car	e Unit N	Aemor	y Tool;	EuroQo	l, European	Health
Index; FIM, Functional Inde	penden	ice Mea	sure;					
Primary outcomes								
Delirium-free days								
Our primary outcome will be	e deliri	um-free	days ov	ver a 14	4-day p	eriod, w	ith delirium	assessed
using the Confusion Assessm	nent M	ethod fo	or the In	tensive	e Care I	Unit (CA	M-ICU) flo	w sheet.
		r featur	es, namo	ely fluc	ctuation	of ment	tal status, ina	
The CAM-ICU is comprised	of fou	I Ioutur		•				attention,
The CAM-ICU is comprised altered level of consciousnes	of fou	disorga	nised th	inking.	CAM-	ICU wa	s commonly	attention, adopted in
The CAM-ICU is comprised altered level of consciousnes ICU settings to measure deli	of fou s, and rium ai	disorgan nd was n	nised th reported	inking. to hav	CAM- ve good	ICU was	s commonly er reliability	attention, adopted in (overall

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1 2	
3	
4 5	
6	
7 8	
9	
10	
12	
13	
14	
16	
17	
19 20	
20 21	
22	
23 24	
25	
20 27	
28	
29 30	
31	
32 33	
34	
35 36	
37	
38 39	
40	
41 42	
43	
44 45	
46	
47 48	
49	
50 51	
52	
53 54	
55	
56 57	
58	
59 60	

1	Secondary outcomes
2	Delirium incidence, duration and severity
3	Delirium incidence refers to the number of patients exhibiting delirium. Delirium duration is
4	calculated from the initial delirium diagnosis to the last assessment indicating the absence of
5	delirium, based on CAM-ICU evaluations conducted every eight hours during the patient's stay.
6	Delirium duration will be measured for each shift and summarized in days. Delirium Severity
7	will be measured by CAM-ICU-7 Delirium Severity Scale, which is a 7-point rating scale
8	derived from the CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments. The
9	final CAM-ICU-7 score ranges from 0-7 with 7 being most severe. CAM-ICU-7 scores are
10	further categorised as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium.
11	CAM-ICU-7 showed a high internal consistency (Cronbach's $a = 0.85$ ) and good correlation with
12	Delirium Rating Scale-Revised - 98 (DRS-R-98) (correlation coefficient = 0.64)(27). The highest
13	CAM-ICU-7 score recorded over the 14-day period will represent delirium severity.
14	RCSQ
15	The Richards-Campbell Sleep Questionnaire (RCSQ) is employed to assess the sleep
16	quality of ICU patients. Originally developed for evaluating sleep in critically ill patients, this
17	questionnaire is designed to capture various aspects of sleep during the ICU stay. The scale
18	evaluates perceptions of sleep depth, sleep onset latency, number of awakenings, time spent
19	awake, and overall sleep quality. The content validity of the Chinese version of the RCSQ
20	questionnaire is 0.840, and the Cronbach's $\alpha$ coefficient is 0.874.
21	PTSD
22	The 17-item PTSD Checklist (PCL) correspond to the DSM-III-R symptoms of PTSD and serves
23	as a self-report scale for assessing PTSD(28,29). Patients will be asked to rate their agreement
24	with each item on a scale from one (not at all) to five (extremely). PTSD-symptoms are

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1	categorized into re-experiencing (flashback, nightmare, emotional cue reactivity, and physical
2	cue reactivity), avoidance and emotional numbing (avoidance of thoughts and reminders,
3	amnesia, loss of interest, detachment, restricted affect, and foreshortened future), and
4	hyperarousal (irritability/anger, sleep disturbance, difficulty concentrating, hypervigilance,
5	exaggerated startle response). The total score ranges from 17 to 85(30).
6	A previous study confirmed the good reliability and validity of the PCL, including test-
7	retest reliability of 0.96, internal consistency reliability of 0.94, and predictive validity of
8	0.64(31). High correlations with the Symptom Checklist-90 further confirm its reliability and
9	validity(32).
10	ICU memory
11	The ICU-Memory Tool (ICU-M) will be used to measure ICU patients' ICU experience(33).
12	This tool includes 14 questions (five open-ended questions and nine closed-ended questions),
13	and is primarily divided into three parts: memories before admission to the ICU; memories
14	during the ICU stay and memories after transferring out of the ICU. Memories during the ICU
15	stay are categorized into three subscales: factual memories (lights, alarms, voices, families,
16	faces, breathing tube, suctioning, darkness, clock, tube in your mouth, and wound care),
17	memories of feelings (discomfort, confusion, sadness, anxiety/fear, panic, and pain), and
18	memories of delusions (feeling that people were trying to hurt you, hallucinations, nightmares.
19	dreams) The total number of memories in each of the three subscales will be summed. The
20	Chinese version of ICU-M has a Cronbach's $\alpha$ coefficient of 0.823 and a scale-level content
20	validity index of 0.046 confirming its good reliability and validity(24)
21	valuaty muck of 0.940, commining its good reliability and valuaty(34).

#### **BMJ** Open

1	Patients' clinical outcomes
2	Medical outcomes will be extracted by the outcome assessor from the electronic health care
3	system upon participants' discharge. This information includes: (a) ICU length of stay: the total
4	number of days a patient stays in ICU; (b) 30-day mortality: the total death cases among all
5	eligible cases at 30 days after admission to ICU; (c) duration of mechanical ventilation: the
6	registered time in hours that the patients are on the mechanical ventilator; (d) the duration of use
7	of physical restraint: the recorded time in hours that the patients are receiving physical restraint;
8	(e) sedation use: the documented total amount and average doses (mg/ per day) of sedation by
9	using the conversion measurement of the same quantity of dexmedetomidine. (f) analgesics use:
10	the documented total amount and average doses (mg/ per day) of analgesics using the conversion
11	measurement of the same quantity of propofol. (g) self-extubation: the documented amount of
12	self-extubation cases; (h) ICU acquired infection: the documented amount of self-acquired
13	infection cases.
14	Quality of life
15	The EuroQol- 5 Dimension (EQ-5D) will be used to assess the participants' quality of life. It
16	assigns a grade on a scale ranging from 0 (representing the worst possible health status) to 100
17	(representing the best possible health status) based on one question for each of the five
18	dimensions, including mobility, self-care, usual activities, pain/discomfort, and
19	anxiety/depression(35).
20	Independence and cognitive function
21	FIM (Functional Independence Measure) will be used to measure both the independence and
22	cognitive function. The FIM is comprised of 18 items, which are grouped into two subscales:

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

are adapted from the Barthel Index and are collectively

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

motor and cog	nition. The m	notor items
known as the l	Motor-FIM. 7	These items
body), Dressir	ng (lower bod	y), Toiletin
(bed/chair/whe	eelchair), Tra	nsfers (toil
The cognition	subscale, kno	own as the
Comprehensio	n, Expression	n, Social in
scored on a 7	7-point ordi	nal scale,
indicates gre	ater indeper	ndence in
Inter-Rater Re	liability of Fl	M has been
with Intraclass	s corelation co	oefficients
Barthel Index	(ICC > 0.83)	have demo
Barthel Index	and items on	the FIM th
Sociodemogra	phic and clin	ical inform
Sociodemogra	phic and clin	ical inform
gender, educat	tional level, n	narital statu
family caregiv	ers, and the h	ealth histor
	Table 2 Con	tent of pro
Session	Content	
Pre-	Clarify Team	Define roles
Implementation	Member Roles	testing, case
		implementat
		supervision
	For peer revie	ew only - http

known as the Motor-FIM. These items includes: Eating, Grooming, Bathing, Dressing (upper
body), Dressing (lower body), Toileting, Bladder management, Bowel management, Transfers
(bed/chair/wheelchair), Transfers (toilet), Transfers (bath/shower), Walk/wheelchair, and Stairs.
The cognition subscale, known as the Cognitive-FIM, includes the following items:
Comprehension, Expression, Social interaction, Problem solving, and Memory. Each item is
scored on a 7-point ordinal scale, ranging from a score of 1 to 7. A higher score
indicates greater independence in performing the task associated with that item. The
Inter-Rater Reliability of FIM has been established with acceptable psychometric performance,
with Intraclass corelation coefficients ranging from 0.86 to 0.88. Concurrent validity with the
Barthel Index (ICC $> 0.83$ ) have demonstrated strong construct validity between items on
Barthel Index and items on the FIM the measure functional limitations (36).
Sociodemographic and clinical information
Sociodemographic and clinical information including ICU patients and family caregivers' age,
gender, educational level, marital status, occupation, the relationship between ICU patients and

istory of ICU patients will be collected. family caregiver 

#### process evaluation and intervention integrity Т

Session	Content	Content Description
Pre-	Clarify Team	Define roles for team members including software requirements, software
Implementation	Member Roles	testing, case selection, recruitment, intervention training, intervention
		implementation, outcome assessment, data management, statistics, and
		supervision personnel.

Page 17 of 28

Session	Content	Content Description
	Organize Research Member Training	Provide standardised training for intervention personnel to ensure consistency in the intervention program.
	Prepare Materials	Develop intervention implementation guidelines, flowcharts, intervention logs, and intervention checklists.
Implementation	Detailed Recording	Record the implementation process and any omissions using intervention logs.
	Supervision Auditing	Conduct process audits of the intervention by a nurse manager not involved in the research.
	Regular Reporting	Provide regular project progress reports, assess the evaluation, and make necessary research adjustments.
	Fidelity	Assess the adherence to intervention elements, dosage, and protocols.
Post- Implementation	Standardized Information Management	Double-check and enter follow-up questionnaires.
	Identify and Correct Errors	Correct errors by manually checking the original dataset, using box plots, histograms, and scatter plots, and using descriptive statistics.
	Handling Missing Data	Supplement missing data through participant contact and medical record queries.
	Analyze Statistic Differences	Compare observed and unobserved statistical differences.

2 2	
ر ۸	
4 5	
5	
7	
/ 0	
0	
9 10	
10	
11	
12	
13	
14	
15	
10	
1/	
18	
19	
∠∪ ว1	
∠ I כר	
22	
23	
24	
25	
20	
27 20	
20	
29	
21	
27	
22	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	

1

Session	Content	Content Description
	Use Intention-	Perform analysis using the intention-to-treat approach.
	to-Treat (ITT)	
	Analysis	

#### Data collection

1

2

3 Two research assistants, both trained consistently, will commence by explaining the study and obtaining written informed consent from the participants. Subsequently, an ICU nurse 4 5 with a master's degree and a postgraduate student specializing in nursing will gather patients' demographic data from their medical records and collect information on their quality of life, 6 independence, and cognitive function prior to admission to the ICU from the participants' family 7 caregivers. The nurses in charge of the study ICU will assess the CAM-ICU, RASS, RCSQ 8 9 during daily routine. On the fourteenth day of a patient's ICU hospitalization, or upon discharge if the ICU stay is less than 14 days, the research assistant will collect data on secondary measures 10 (PTSD, ICU memory), clinical outcomes, independence, and cognitive function. Additionally, 11 12 quality of life, independence, and cognitive function will be assessed via a phone call by the research assistant six months after the completion of the intervention. Notably, 13 14 Two research centers each have two research assistants dedicated to obtaining informed consent 15 and collecting data, respectively. 16 **Data management** 17 Each patient has a case report form (CRF) for data collection, initially documented on paper. 18

- 19 Following this, the data from the CRFs are transferred to Excel spreadsheets on computers.
- 20 Access to the Excel files will be restricted through password protection. Only authorized
- 21 personnel participating in the study will have access to these files. All data entry and
- 22 manipulation activities will be logged and tracked to maintain transparency and accountability.

Page 19 of 28

#### **BMJ** Open

To identify and rectify errors, such as missing values, outliers, and typos, data cleaning strategies will be employed(37). Several methods will be employed to detect errors and minimise the impacts on the accuracy of results. Firstly, the original dataset (in Excel) will be manually checked to identify data error. Secondly, statistical graphical explorations including box plots, histograms and scatter plots, along with descriptive statistics such as mean, frequency, and percentage, will be used. Through this process, data errors, including typos, outliers, and violations of integrity constraints, will be corrected. **Data analysis** This study will utilize R4.3.2 software for data analysis, with statistical analysis led by two master's degree-holding research personnel. All statistical tests will be two-tailed, with the significance level set at 0.05. To assess the normal distribution of continuous variables, skewness, kurtosis, Q-Q plots, and histograms will be examined. Variables with skewness and 

13 kurtosis values within the range of -2.0 to 2.0 will be considered to have a normal distribution.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES)

Enseignement Superieur (ABES). Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

For normally distributed continuous variables, the study will describe them using the mean  $\pm$ 

15 standard deviation (Mean  $\pm$  SD). For variables that do not meet the normal distribution criteria,

- 16 the study will describe them using the median (interquartile range, IQR). Categorical variables
- 17 will be described using frequency (proportion). If the assumptions for hypothesis testing of

18 continuous variables are met, independent two-sample t-tests will be used to compare differences

19 between different groups. Otherwise, the Wilcoxon-Mann-Whitney will be employed. For

20 categorical variables, chi-square tests and Fisher's exact tests will be used to compare differences

- 21 between different groups. Additionally, missing values will be imputed using multiple
- 22 imputation methods. The study will follow the intention-to-treat (ITT) and per-protocol (PP)
- 23 principle for analysis. After imputing missing data using multiple imputation methods, the study

#### Page 20 of 28

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) .

Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

#### **BMJ** Open

will perform ITT and PP analysis and report relevant uncertainty indicators, such as confidence
intervals and standard errors, in the results. This study will employ mixed-effects models for
outcomes with repeated measurements. These models, also known as multilevel or hierarchical
models, are effective for analyzing data with a hierarchical structure, such as repeated
measurements. Fixed effects will estimate population-level relationships between predictors and
outcomes. Our study will include predictors like APACHE-II score, age, admission category, and
use of sedatives and analgesics as fixed explanatory variables. Subgroup analyses based on age,
gender, and length of ICU stay will be conducted.

#### **DISCUSSION**

This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function). It employs a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention within ICUs, which enhances the reliability and validity of findings. The methodological rigor of this design provides valuable insights into the effectiveness of such interventions in clinical settings. In our study, our primary focus is on preventing delirium. However, if delirium does occur,

In our study, our primary focus is on preventing delirium. However, if delirium does occur,
physicians may prescribe antipsychotic medications. We will accurately document whether
patients receive these medications and the dosage administered. Furthermore, we will maintain
detailed records of the dosage of sedatives and analgesics administered to patients throughout the
study.

#### BMJ Open

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.	J Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I
---	---

Π

1	Due to the nature of the intervention, blinding was only possible for the outcome assessors, while
2	blinding for the participants and those delivering the intervention was not feasible.
3	The study anticipates prompt availability of materials from family members and has contingency
4	plans in place to ensure timely initiation of the VR intervention. However, delays in obtaining
5	materials from family members may occur, potentially impacting the initiation of the VR
6	intervention. Additionally, the use of antipsychotic medications to manage delirium may
7	influence study outcomes, and while their administration will be documented, their effects on
8	study outcomes may not be fully controlled.
0	Funding statement
)	
10	This study has received support from the China Postdoctoral Science Foundation
11	(2023M731551) and the Science and Technology Project of Shenzhen
12	(JCYJ20230807142300002).
13	Competing interests statement
14	The authors declare that they have no competing interests.
15	
16	Patient and Public Involvement
17	Patients or the public were not involved in the design, or conduct, or reporting, or
18	dissemination plans of our research.
19	
20	Contributors
20	SI VI DI ET designed the study and wrote the manuscript SI is the principal investigator
21	and data management leader MH TW and VL are members of the study team who contributed
22	to the development of the study methods, and team members supervised the trial. All outhors
23 24	approved the final version of the manuscript.
	21

1		
2		
4	1	
5		
6	•	
7	2	word counts: 3453
8		
9 10	2	Figure 1: Diagram of the flow of the study
11	3	Figure 1. Diagram of the now of the study
12		
13	4	Figure 2: Flowchart of VR-based sensory stimulation implementation
14 15	т	rigure 2. riowenart of vic bused sensory summation implementation
16	5	
17	-	
18		
19 20	6	References
20	_	
22	7	I. Jayaswal AK, Sampath H, Soohinda G, Dutta S. Delirium in medical intensive
23	8	care units: Incidence, subtypes, risk factors, and outcome. Indian J Psychiatry, 2019:61(4):352–
24		
26	9	8.
27	10	2 Gravante E. Giannarelli D. Pucci A. Gagliardi AM. Mitello I. Montagna A. et al
28	10	2. Gravance I, Grannaren D, I deer A, Gagnardi Alvi, Witcho E, Wontagna A, et al.
29 30	11	Prevalence and risk factors of delirium in the intensive care unit: An observational study. Nurs
31	10	Crit Corro 2021 Max 26(2):156 (5
32	12	Crit Care. 2021 May, 20(3):130–05.
33	13	3. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FEJ, et al.
34 35		
36	14	Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.
37	15	JAMA 2004 Apr 291(14) 1753–62
38		
39 40	16	4. Liang S, Chau JPC, Lo SHS, Bai L, Yao L, Choi KC. Validation of PREdiction of
41	17	DELIRium in ICu patients (PRE-DELIRIC) among patients in intensive care units: A
42	1/	DELINIUM IN ICU patients (I RE-DELINIC) among patients in intensive care units. A
43 44	18	retrospective cohort study. Nursing in Critical Care. 2021 May;26(3):176-82.
44	10	5 Maleta G. Carala D. Dardin, IW. Churchille V. Marada M. Farraranan, D. et al.
46	19	5. Menta S, Cook D, Devlin JW, Skrobik Y, Meade M, Fergusson D, et al.
47	20	Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. Crit Care
48		
50	21	Med. 2015 Mar;43(3):557–66.
51	22	6 Wolters AE Peelen LM Welling MC Kok L de Lange DW Cremer OL et al
52		
53 54	23	Long-Term Mental Health Problems After Delirium in the ICU. Crit Care Med. 2016
55	24	Oct: 44(10): 1808 = 13
56	2 <b>4</b>	ооцтт(10).1000-15.
57 58		22
50 59		
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 23 of 28

#### **BMJ** Open

1 2		
- 3 4	1	7. Liang S, Chau JPC, Lo SHS, Zhao J, Choi KC. Effects of nonpharmacological
5 6	2	delirium-prevention interventions on critically ill patients' clinical, psychological, and family
7 8	3	outcomes: A systematic review and meta-analysis. Australian Critical Care. 2021 Jul;34(4):378-
9 10	4	87.
11 12	5	8. Liang S, Chau JPC, Lo SHS, Choi KC, Bai L, Cai W. The effects of a sensory
13 14	6	stimulation intervention for preventing delirium in a surgical intensive care unit: A randomized
15 16	7	controlled trial. Nursing in Critical Care. 2023 Sep;28(5):709–17.
17 18	8	9. Liang S, Pak Chun Chau J, Hoi Shan Lo S, Chow Choi K, Bai L, Cai W. The
19 20	9	effects of a sensory stimulation intervention on psychosocial and clinical outcomes of critically
21 22	10	ill patients and their families: A randomised controlled trial. Intensive and Critical Care Nursing.
23 24	11	2023 Apr;75:103369.
25 26	12	10. Strøm BS, Ytrehus S, Grov EK. Sensory stimulation for persons with dementia: a
27 28	13	review of the literature. J Clin Nurs. 2016 Jul;25(13–14):1805–34.
29 30	14	11. Moattari M, Alizadeh Shirazi F, Sharifi N, Zareh N. Effects of a Sensory
31 32	15	Stimulation by Nurses and Families on Level of Cognitive Function, and Basic Cognitive
33 34	16	Sensory Recovery of Comatose Patients With Severe Traumatic Brain Injury: A Randomized
35 36	17	Control Trial. Trauma Mon. 2016 Sep;21(4):e23531.
37 38	18	12. Liang S, Chau JPC, Lo SHS, Zhao J, Liu W. Non-pharmacological delirium
39 40	19	prevention practices among critical care nurses: a qualitative study. BMC Nurs. 2022 Aug
41 42	20	25;21(1):235.
43 44	21	13. Liang S, Chau JPC, Lo SHS, Li S, Gao M. Implementation of ABCDEF care
45 46	22	bundle in intensive care units: A cross-sectional survey. Nursing in Critical Care. 2021
47 48	23	Sep;26(5):386–96.
49 50	24	14. Luan L, Ding M. Progress in the application of virtual reality technology in
50 51 52	25	critically ill patients in ICU. Chinese Journal of Nursing. 2021 Aug 15;56(8):1255.
52 53 54	26	15. Jawed YT, Golovyan D, Lopez D, Khan SH, Wang S, Freund C, et al. Feasibility
54 55 56	27	of a virtual reality intervention in the intensive care unit. Heart Lung. 2021;50(6):748-53.
57 58		23
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 24 of 28

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

1

60

2 3	1	16 Ong TL. The DREAMS Project: Improving the Intensive Care Patient Experience
4 5	1	with Virtual Deality [Internet] [aited 2022 Oct 12] Available frame
6	2	with virtual Reality [Internet]. [cited 2023 Oct 13]. Available from:
8	3	https://arx1v.org/abs/1906.11706
9 10	4	17. Ong TL, Ruppert MM, Akbar M, Rashidi P, Ozrazgat-Baslanti T, Bihorac A, et
11 12	5	al. Improving the Intensive Care Patient Experience With Virtual Reality-A Feasibility Study.
13 14	6	Crit Care Explor. 2020 Jun;2(6):e0122.
15	7	18. Restorative effects of virtual nature settings - PubMed [Internet]. [cited 2023 Oct
10 17	8	13]. Available from: https://pubmed.ncbi.nlm.nih.gov/20950174/
18 19 20	9	19. Ohly H, White MP, Wheeler BW, Bethel A, Ukoumunne OC, Nikolaou V, et al.
20 21 22	10	Attention Restoration Theory: A systematic review of the attention restoration potential of
22 23 24	11	exposure to natural environments. J Toxicol Environ Health B Crit Rev. 2016;19(7):305-43.
24 25 26	12	20. Chirico A, Cipresso P, Yaden DB, Biassoni F, Riva G, Gaggioli A. Effectiveness
27	13	of Immersive Videos in Inducing Awe: An Experimental Study. Sci Rep. 2017 Apr
20 29 20	14	27;7(1):1218.
30 31 22	15	21. Toyabe S ichi, Kouhei A. Referral from secondary care and to aftercare in a
33 34	16	tertiary care university hospital in Japan. BMC Health Services Research. 2006;6(1):11.
35 36	17	22. Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S, et al.
37 38	18	Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond
39 40	19	Agitation-Sedation Scale (RASS). JAMA. 2003 Jun;289(22):2983-91.
40 41 42	20	23. Moon K, Lee S. The effects of a tailored intensive care unit delirium prevention
42	21	protocol: A randomized controlled trial. International journal of nursing studies.
44 45	22	2015;52(9):1423–32.
46 47	23	24. Mailhot T, Cossette S, Côté J, Bourbonnais A, Côté MC, Lamarche Y, et al. A
48 49	24	post cardiac surgery intervention to manage delirium involving families: a randomized pilot
50 51	25	study. Nursing in critical care. 2017 Jul;22(4):221-8.
52 53		
54 55		
56 57		24
58 59		

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 25 of 28

1

60

#### BMJ Open

2		
3 4	1	25. Munro C, Cairns P, Ji M, Calero K, Anderson W, Liang Z. Delirium prevention in
5 6	2	critically ill adults through an automated reorientation intervention - A pilot randomized
7 8	3	controlled trial. Heart & Lung - The Journal of Acute and Critical Care. 2017;46(4):234-8.
9 10	4	26. Zou J. Reliability and validity test of Chinese version of CAM-ICU and
11 12	5	comparison with other scales. Huazhong University of Science and Technology; 2012.
12 13 14	6	27. Babar A. Khan, Perkins Anthony J, Sujuan Gao, Siu L. Hui, Campbell L. Noll,
14 15 16	7	Farber Mark O, Chlan Linda L BMA, Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, et al.
10 17 19	8	The CAM-ICU-7 Delirium Severity Scale: A novel delirium severity instrument for use in the
10 19 20	9	Intensive Care Unit. Critical care medicine. 2017;45(5):851–7.
20 21 22	10	28. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist
22 23 24	11	(PCL): Reliability, Validity, and Diagnostic Utility. New York: Guilford Press; 1993.
24 25 26	12	29. Mollica RF, Caspi-yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard
20 27 28	13	trauma questionnaire: Validating a cross-cultural instrument for measuring torture, trauma, and
20 29 30	14	posttraumatic stress disorder in indochinese refugees. The journal of nervous and mental disease.
30 31 20	15	1992;180(2):111–6.
33 34	16	30. Svenningsen H, Egerod I, Christensen D, Tonnesen EK, Frydenberg M, Videbech
35 36	17	P. Symptoms of posttraumatic stress after intensive care delirium. BioMed Research
37 38	18	International. 2015;
39 40	19	31. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric
40 41 42	20	properties of the PTSD checklist (PCL). Behaviour research and therapy. 1996;34(8):669-73.
42 43	21	32. Yang L, Yang X, Yang H, Liu Q. Study on the validity, reliability and influencing
44 45 46	22	factors of the civilian version of the Post-traumatic Stress Checklist. Chinese Journal of Health
40 47 49	23	Psychology. 2007;15(1):6-9.
48 49	24	33. Jones C, Humphris G, Griffiths RD. Preliminary validation of the ICUM tool: a
50 51	25	tool for assessing memory of the intensive care experience. Clinical Intensive Care.
52 53 54	26	2000;11(5):251–5.
55 56 57		25
58 59		

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

#### **BMJ** Open

1	34.	Huang L, Jiang Q, Lin X, Hou W, Wang S, Wang X. The reliability and validity				
2	test of ICU N	Iemory Scale. Chinese Journal of Nursing. 2016;51(10):1265–9.				
3	35.	Balestroni G, Bertolotti G. [EuroQol-5D (EQ-5D): an instrument for measuring				
4	quality of life	e]. Monaldi Arch Chest Dis. 2012 Sep;78(3):155-9.				
5	36.	Parallel reliability of the functional independence measure and the Barthel ADL				
6	index - PubMed [Internet]. [cited 2023 Oct 13]. Available from:					
7	https://pubmed.ncbi.nlm.nih.gov/11117590/					
8	37.	Van Den Broeck J, Cunningham SA, Eeckels R, Herbst K. Data cleaning:				
9	Detecting, di	agnosing, and editing data abnormalities. PLoS medicine. 2005;2(10):966-70.				
10						



Page 28 of 28







359x288mm (72 x 72 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# **BMJ Open**

### Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-083966.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Oct-2024
Complete List of Authors:	Liang, Surui; Tung Wah College; Shenzhen Hospital of Southern Medical University Liu, Yong; Shenzhen Hospital of Southern Medical University, Intensive Care Unit Wen, Taoxue; Shenzhen Hospital of Southern Medical University, Luo, Dan; Shenzhen Hospital of Southern Medical University, Intensive Care Unit he, mingxin; Peking University Shenzhen Hospital, Tian, Jinfei; Shenzhen Hospital of Southern Medical University, Intensive Care Unit
<b>Primary Subject Heading</b> :	Nursing
Secondary Subject Heading:	Neurology
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, INTENSIVE & CRITICAL CARE, Virtual Reality

## SCHOLARONE<sup>™</sup> Manuscripts

Page 1 of 26

2 3 4	1	Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing								
5 6 7	2	Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol								
8	3	Authors: Surui Liang <sup>1*</sup> , PhD; Yong Liu <sup>1</sup> , PhD; Taoxue Wen <sup>1</sup> , MM; Dan Luo <sup>1</sup> , MM;								
9 10	4	Xinming He <sup>2</sup> , MM; Jinfei Tian <sup>1</sup> , MM.								
11 12	5	Address 1: Department of Intensive Care Unit, Shenzhen Hospital of Southern Medical								
13	6	University, Shenzhen, Guangdong, China								
14 15	7	Address 2: Department of Intensive Care Unit, Peking University Shenzhen Hospital,								
16 17	8	Shenzhen, Guangdong, China								
18 10	9	*: Corresponding author								
20	10	Surui Liang liangsurui@link.cuhk.edu.hk/liangsr5@mail2.sysu.edu.cn								
21 22	11	Yong Liu <u>liuyongjoy@outlook.com</u>								
23 24	12	Taoxue Wen <u>wtx_2024@126.com</u>								
25 26	13	Dan Luo <u>luodan0325@hotmail.com</u>								
27	14	Mingxin He <u>695318082@qq.com</u>								
28 29	15	Jinfei Tian <u>18907287566@163.com</u>								
30 31	16	Corresponding author: Surui Liang								
32 33	17	Address: Department of Intensive Care Unit, Shenzhen Hospital, Southern Medical								
34	18	University, Shenzhen, Guangdong, China								
35 36	19	Telephone: (86) 17801305403Email: liangsr5@mail2.sysu.edu.cn								
37 38	20	Contributors LSR, LY, WTX, LD, HMX, and TJF contributed to the study's conception and								
39 40	21	design. LSR led data management as the principal investigator, while HMX, WTX, and LY								
41	22	developed the study methods and provided supervision. All authors participated in drafting								
42 43	23	and revising the manuscript. LSR is the guarantor responsible for the integrity of the study.								
44 45 46	24	All authors approved the final manuscript and agreed to be accountable for the work.								
47	25	Funding This study has received support from the China Postdoctoral Science Foundation								
40 49	26	(2023M731551) and the Science and Technology Project of Shenzhen								
50 51 52	27	(JCYJ20230807142300002).								
53 54	28	Competing interests None declared.								
55 56	29	Patient consent for publication Not required.								
57	30 <b>Ethics approval</b> This protocol was approved by Research Ethics Committee of Shenzhen									
58 59 60	31	Hospital of Southern Medical University (NYSZYYEC20230068).								

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Trial registration number ClinicalTrials.gov NCT06153472. Trial registration date: 

- November 22, 2023
- Version of the trial protocol, date, and version identifier: 2023K089; Verification Date: April
- 2024; version identifier: Version 1.
- This study has received support from the China Postdoctoral Science Foundation
- (2023M731551) and the Science and Technology Project of Shenzhen
- (JCYJ20230807142300002). No intervention is conducted by the sponsors in the research
- design, data collection, management, analysis and interpretation of data, report writing,
- publication, etc. to occurrence of the terms of terms

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

**BMJ** Open

2 3	1									
4 5	1									
6	2	ABSTRACT								
8	3	Introduction:								
9 10 11	4	Delirium is a common acute cognitive impairment characterized by confusion, disorientation,								
12 13	5	and attention deficits, particularly prevalent in ICU settings. Given its significant impact on								
14 15	6	patients, caregivers, and healthcare resources, preventing delirium in ICU patients is of								
16 17 18	7	paramount importance. This is the first randomized controlled trial (RCT) designed to								
19 20	8	evaluate the effects of a Virtual Reality-based sensory stimulation intervention on preventing								
21 22	9	delirium in intensive care unit (ICU) patients.								
23 24 25	10	Methods and Analysis:								
25 26 27	11	We employed a paired randomization method to match eligible participants based on a								
28 29	12	validated delirium risk scoring model for ICU patients. The study will commence in								
30 31	13	September 2024 and conclude in June 2026. A consecutive sample of 324 ICU patients								
32 33 34	14	admitted to the study setting will be recruited. Eligible participants will be randomly								
35 36	15	allocated to receive either Virtual Reality-based sensory stimulation in addition to usual care								
37 38	16	or usual care alone. The Virtual Reality-based sensory stimulation intervention will last for								
39 40 41	17	up to fourteen days, with all interventions administered by a research team. We define								
42 43	18	delirium-free days over a 14-day period as the primary outcome. The secondary outcomes								
44 45	19	will include delirium incidence, duration, and severity, patients' psychological well-being								
46 47	20	(post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes,								
48 49 50	21	and other outcomes (quality of life, independence, and cognitive function). Data will be								
51 52	22	collected at baseline, post-intervention, and six months post-intervention. Two independent t-								
53 54	23	tests or Wilcoxon-Mann-Whitney tests will be utilized for continuous variables, while chi-								
55 56 57 58 59	24	square or Fisher's exact tests will be employed for categorical variables. The analysis will								

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

adhere to both the intention-to-treat and per protocol principles. Additionally, mixed-effects models and subgroup analysis will be planned. **Ethics and dissemination** This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068). All participants or their family caregivers will provide written informed consent. Results will be disseminated through scientific publications, and presentations at local and international conferences. Trial registration number ClinicalTrials.gov NCT06153472. Trial registration date: November 22, 2023 Word counts: 232 Keywords: Critical care; Delirium, Virtual Reality, Sensory stimulation **Article Summary** Strengths and limitations of this study ► This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function). ► This study utilizes a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention for preventing delirium in ICUs. The methodological rigor of this design enhances the reliability and validity of our findings, providing valuable insights into the effectiveness of such interventions in clinical settings. ▶ Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible. 

#### BMJ Open

1	INTRODUCTION
2	Delirium is a common acute state of cognitive confusion. Intensive Care Unit (ICU)
3	delirium is highly prevalent, with an incidence ranging from 31%[1] to 56%[2], and it can be as
4	high as 81%[3] in ICU patients undergoing mechanical ventilation. A preliminary analysis of
5	data from 375 patients admitted to the ICU for more than 24 hours revealed an occurrence rate of
6	44% for ICU delirium[4]. Moreover, delirious ICU patients had 1.33 times longer ICU stays and
7	a 9.57-fold increase in mortality compared to non-delirious ICU patients[5]. ICU patients who
8	experience delirium may suffer from post-traumatic stress disorder, anxiety, depression, and
9	cognitive impairment for up to two years[6].
10	Non-pharmacological preventive measures aim to reduce one or more modifiable risk
11	factors for ICU delirium[7]. Previous research identified sensory stimulation as a key and
12	effective non-pharmacological intervention in preventing ICU delirium[8,9]. Sensory stimulation
13	involves activating one or more senses[10], with visual and auditory stimuli being particularly
14	effective for ICU patients[11]. To further investigate the effectiveness of sensory stimulation in
15	preventing ICU delirium, the research team conducted an initial study to assess the
16	implementation of sensory stimulation on preventing delirium in ICU and subsequently
17	developed a sensory stimulation intervention plan[12,13]. This plan involved daily sessions of 30
18	minutes each for seven days, including visual stimuli (displaying personal or family photos) and
19	auditory stimuli (playing recordings of family members). The results of the study showed that
20	sensory stimulation reduced the duration and severity of ICU delirium but did not significantly
21	decrease the incidence of ICU delirium[8,9]. The limited effectiveness of sensory stimulation
22	may be attributed to the narrow range of stimuli, insufficient stimulus intensity, and inadequate
23	dosing and implementation methods[9].

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1	In contrast, Virtual Reality (VR) technology, characterized by its three-dimensional and
2	highly immersive qualities, has the potential to provide more effective sensory stimulation by
3	immersing participants in three-dimensional dynamic environments[14]. International researches
4	[15–17] suggest that VR offers significant advantages in sensory stimulation and could be a
5	promising approach for preventing ICU delirium. However, it is important to note that studies on
6	the use of VR in this context are still in the feasibility testing stage. The DREAMS project at the
7	University of Florida in the United States investigated the effectiveness of VR and found that
8	95.6% of participants found it very comfortable, 51.9% reported improved sleep quality, and
9	81.5% experienced reduced pain[16]. This team further conducted a study with 46 ICU patients,
10	implementing a seven-day VR intervention, which resulted in reduced stress, pain, anxiety, and
11	improved cognitive function and attention in the participants[17]. Additionally, Jawed and
12	colleagues conducted a preliminary trial that showed VR could alleviate anxiety in ICU
13	patients[15]. However, since those studies were in the feasibility testing stage, they were unable
14	to measure the effects on reducing ICU delirium.
15	The stress recovery theory and attention restoration theory explain the principles behind
16	preventing ICU delirium using VR-based sensory stimulation[18,19]. The stress recovery theory
17	suggests that natural environments support positive changes in emotional states and
1/	suggests that natural environments support positive enanges in emotional states and
18	psychophysiological recovery, primarily by relaxing the parasympathetic nervous system [19].
19	In stressful ICU environments, cognitive and attentional resources can become fatigued, which is
20	especially crucial for critically ill patients facing stressors. The cognitive demands and
21	overstimulation in the ICU environment contribute to mental fatigue and stress responses[19].
22	On the other hand, the attention restoration theory suggests that exposure to natural environments
23	requires fewer cognitive resources and promotes a sense of disengagement from stressors,
	6

1	allowing attention to rest and recover[18]. Therefore, VR-based visual and auditory stimuli, by						
2	immersing patients in relaxing VR environments, may provide a protective effect against						
3	environmental stress and support the recovery of physiological, emotional, and attentional						
4	functions, thereby helping to prevent delirium. Chirico and colleagues further elucidated the						
5	mechanisms of VR-based sensory stimulation in delirium prevention: exposure to VR-based						
6	natural environments can trigger a specific psychophysiological pattern activated by the						
7	parasympathetic nervous system, leading to intense emotional reactions[20]. Emotion responses						
8	increase with higher levels of immersion, which can be utilized to alleviate symptoms like						
9	anxiety, pain, and fear, effectively reducing patient stress, improving sleep quality, and						
10	consequently reducing the incidence of delirium[20].						
11	Aim and hypothesis						
12	This study aims to evaluate the effects of evaluates a Virtual Reality-based sensory stimulation						
13	on preventing delirium, and improving patients' psychological (post-traumatic stress disorder,						
14	sleep quality, ICU memory), patients' clinical (ICU length of stay) and other outcomes (quality						
15	of life, independence and cognitive function). And the comparator in our study is 'usual care,'						
16	representing the standard treatment or practices typically provided in similar clinical settings.						
17	It is hypothesised that at patients' fourteenth day of ICU hospitalisation or the day of discharge						
18	(if the ICU stay is less than 14 days), will experience the following improvements compared with						
19	those receiving usual care.						
20	1. ICU patients receiving the sensory stimulation intervention will have:						
21	a. A reduction in incidence, duration and severity of delirium.						
22	b. An improvement in their post-traumatic stress disorder.						
23	c. An improvement of factual memories.						
	7						
	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml						

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1										
2										
5 ∕	1	d. A shorter length of ICU stay.								
- 5										
6	2	e. An improvement in quality of life, independence and cognitive function.								
7										
8	3	At six months after completing the intervention, compared to those receiving usual care,								
9										
10	4	ICU patients undergoing the VR-based sensory stimulation intervention will experience an								
11										
12	5	improvement in quality of life, independence, and cognitive function.								
13		r ····· ······························								
14	6	METHODS AND ANALYSIS								
16	Ū									
17	7	Design								
18	,									
19	8	A multi-center assessor-blinded two-arm parallel group RCT will be conducted								
20	0	A mani-center assessor-officied two-arm paranet group ite 1 will be conducted.								
21	0	Sotting								
22	9	Setting								
23	10	Dertiginants will be rearryited from general ICUs of Shanzhen Hagnital of Southern Medical								
24 25	10	Participants will be recluited from general ICOS of Shelizhen Hospital of Southern Medical								
26	11	University and Shenzhen Hospital of Rejijng University, two comprehensive tertiary $\Delta$ -level								
27	11									
28	1.0	hospitals in Shenzhen, Guangdong province, Mainland China. Tertiary A-level hospital provides								
29	12	nospitals in Shenzhen, Guangdong province, Mainland China. Tertiary A-level hospital provides								
30										
31	13	specialist tertiary care in a large nospital after a referrar from primary and secondary care[21].								
32										
33 34	14	Participants								
35		4								
36	15	All ICU patients admitted to the study setting will be recruited if they are/have: (1) aged 18 years								
37										
38	16	or older, (2) first-time admission to the ICU, and (3) a Richmond Agitation-Sedation Scale								
39										
40	17	(RASS) score of $\geq$ -3[22]. Patients will be excluded if they have: (1) been diagnosed with								
41										
42	18	dementia, delirium or acute psychiatric illness at admission, (2) been diagnosed with end-stage								
43 44										
44	19	cancer, (3) severe hearing impairment and cannot be corrected by hearing aids and (4) been								
46										
47	20	admitted to ICU with radioactive material.								
48										
49	21	Sample size determination								
50										
51	22	Sample size calculation for the difference test in delirium incidence between the								
52 52		Sumpre Size eurouweren for die unterenee test in dentrum mendenee between the								
53 54	23	experimental and control groups was performed using $G^*$ Power 3.4. Based on a prior study								
55 55	23	experimental and control groups was performed using G 1 6 well 3.4. Dased on a prior study,								
56										

Page 9 of 26

#### **BMJ** Open

1	delirium incidence after sensory stimulation was 13%, while it was 25% in the standard care						
2	group, yielding an odds ratio of 0.57[8]. For G* Power's two-sample proportion (z-test)						
3	calculation, with a significance level set at $\alpha = 0.05$ and a desired test power of Power = 0.8,						
4	the required sample size was determined to be 259 participants. Additionally, to account for						
5	factors such as patient mortality and loss to follow-up in the ICU, and considering a 20% dropout						
6	rate, this study intends to recruit a total of 324 participants, with 162 participants in each group.						
7	Randomisation and allocation concealment						
8	We employed a simple randomization method by generating random numbers through the						
9	randomization.com website. Based on these generated numbers, participants were then randomly						
10	assigned to either the intervention or control group. To ensure allocation concealment,						
11	consecutively numbered, sealed, and opaque envelopes will be utilized. This process will be						
12	conducted by a research assistant who will have no further involvement in the study after						
13	participant enrollment.						
14	Blinding						
15	Owing to the nature of the intervention, the researchers responsible for delivering the						
16	intervention will be aware of the group assignment. However, the outcome assessors will remain						
17	blinded to the group allocation and will not participate in data analysis or result reporting.						
18	Intervention						
19	Participants allocated to the intervention group will receive a VR-based sensory stimulation						
20	intervention plus usual care. This intervention is designed to provide VR-based visual and						
21	auditory stimulation to ICU patients, with additional support from family caregivers. The						
22	intervention will be administered by researchers who are trained ICU nurses. It will commence						
23	upon the patient's admission and continue until the fourteenth day of their ICU hospitalization or						

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

the day of discharge if their stay is less than 14 days. Each day, a 30-minute session will be conducted [23–25].

The investigator will provide a delirium knowledge leaflet and a sample reorientation message to family caregivers in the intervention group. The investigator will spend 30 minutes explaining the contents to family caregivers during their first meeting. Family caregivers will be asked to prepare the family photographs, family video or recording at their earliest convenience. The leaflet contains information about the definition, prevalence and risk factors of delirium, along with practical steps family caregivers can take to support the patients. These steps include engaging in simple conversations, reminding patients of the current time, date, and location, providing glasses or hearing aids when necessary, decorating patient beds with family photographs, and discussing familiar topics. The reorientation messages serve to help patients understand their surroundings and offer encouragement. Each segment of the message requires two minutes for recording, following the sample message. The leaflet was designed by the investigator, and the sample reorientation message was adapted from a previous study[25]. Both the leaflet and the sample orientation message were reviewed by a committee comprising three ICU nurse specialists, two nurse academics, one physician and two family caregivers. Each daily session will commence at the earliest available daytime hour, typically between 12:00 and 16:00, following the completion of family recordings. During the pre-bedside phase, the investigator will gather family photographs, recordings, and videos, either digitally recorded or retrieved from previous family collections stored on electronic devices. Subsequently, the investigator will spend 30 minutes with each patient in the intervention group, tailoring the intervention based on the patient's ability to engage with auditory or visual stimulation (Figure 1). Notably, the intervention will be discontinued for trial participants under conditions such as participant requests or fluctuations in disease status. 

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 11 of 26

## BMJ Open

1 2												
3 4	1	Implementation Co	ntent: T	he interv	vention	consist	s of the	follow	ving stages:	① Guidance		
5 6 7	2	Stage (2 minutes): Introduc	ing the	content	and pur	pose of	f the VI	R scene	s to be play	yed in the next		
, 8 9	3	30 minutes; 2 Relaxation	n Stage (	(5 minut	tes): Sel	ecting	natural	scener	y VR scene	s accompanied		
10 11 12	4 by soothing background music to help patients relax; ③ Family and Friends Support Sta									port Stage (18		
12 13 14	5	5 minutes): Playing VR scene videos provided by family and friends, selecting happy moments										
15 16	6	and conveying family wish	es and b	olessing	s; ④ F	eedbac	k Stage	e (5 mir	utes): Gui	ding patients to		
17 18 19	7	provide feedback and colle	cting re	levant p	aramete	rs, suc	h as hea	art rate,	respiration	n, pain, etc.		
20 21	8	Control group										
22 23 24	9	Participants in the control g	group w	ill receiv	ve the us	sual ca	re, cons	sistent v	with their e	xisting or		
24 25 26	10	planned treatment routines.	anned treatment routines. Registered ICU nurses will administer the same nursing care, which									
27 28	11	includes, but is not limited to, sedation, analgesia, spontaneous breathing trials, indwelling catheter management, feeding, and bowel care.								dwelling		
29 30 31	12											
32 13 Outcome and outcome measures												
34 35 26	14	The research will measure the following outcomes. See Table 1.										
30 37 38	15	Table 1 Outcomes and time schedules for data collection										
39 40 41		Data Collection Time Points Endpoint								Endpoint		
42 43 44		Outcome Measures							Day14	6 Months		
45 46			Day1	Day2	Day3				Discha rge	Discharge		
47 48 49		Delirium Score (CAM- ICU)	Х	Х	Х				X			
50 51		Sedation Score (RASS)	Х	Х	Х				Х			
52 53		Pain Score (NRS)	Х	Х	Х				Х			
54 55		Pain Score (BPAT)	Х	Х	Х				Х			
56 57		Sleep (RCSQ)				11						
58 59								,				
60		For peer revi	ew only -	http://bn	njopen.bi	mj.com/	'site/abo	ut/guide	elines.xhtml			

2										
3		X X X X X								
4		Post-traumatic stress								
5 6		disorder (PCL) X								
7 8		ICU Memory (ICUMT) X								
9 10		Patient Clinical Outcomes X								
11 12		Quality of Life Score (EuroQol)XXX								
13 14		Independence Function (motor-FIM) X X X								
15 16		Cognitive function (cognitive-FIM) X X X								
17 18	1	Note: CAM-ICU, Confusion Assessment Methods for Intensive Care Units; RASS,	-							
19 20	2	Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPAT, behavior pain								
21 22	3	assessment tool; RCSQ, Richards-Campbell Sleep Questionnaire; PCL, Posttraumatic Stress								
23 24	4	Disorder Checklist; ICUMT, Intensive Care Unit Memory Tool; EuroQol, European Health								
25 26	5	Index; FIM, Functional Independence Measure;								
27 28	6	Primary outcomes								
29 30 31	7	Delirium-free days								
32 33	8	Our primary outcome will be delirium-free days over a 14-day period, with delirium assessed								
34 35	9	using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) flow sheet.								
36 37	10	The CAM-ICU is comprised of four features, namely fluctuation of mental status, inattention,								
38 39 40	11	altered level of consciousness, and disorganised thinking. CAM-ICU was commonly adopted in								
41 42	12	ICU settings to measure delirium and was reported to have good interrater reliability (overall								
43 44	13	kappa coefficient = $0.71$ )[26].								
45 46 47	14	Secondary outcomes								
47 48 49	15	Delirium incidence, duration and severity								
50 51	16	Delirium incidence refers to the number of patients exhibiting delirium. Delirium duration is								
52 53	17	calculated from the initial delirium diagnosis to the last assessment indicating the absence of								
54 55 56	18	delirium, based on CAM-ICU evaluations conducted every eight hours during the patient's stay.								
50 57 59		12								
50 59										
1	Delirium duration will be measured for each shift and summarized in days. Delirium Severity									
----	---									
2	will be measured by CAM-ICU-7 Delirium Severity Scale, which is a 7-point rating scale									
3	derived from the CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments. The									
4	final CAM-ICU-7 score ranges from 0-7 with 7 being most severe. CAM-ICU-7 scores are									
5	further categorised as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium.									
6	CAM-ICU-7 showed a high internal consistency (Cronbach's $a = 0.85$ ) and good correlation with									
7	Delirium Rating Scale-Revised - 98 (DRS-R-98) (correlation coefficient = 0.64)[27]. The highest									
8	CAM-ICU-7 score recorded over the 14-day period will represent delirium severity.									
9	RCSQ									
10	The Richards-Campbell Sleep Questionnaire (RCSQ) is employed to assess the sleep									
11	quality of ICU patients. Originally developed for evaluating sleep in critically ill patients, this									
12	questionnaire is designed to capture various aspects of sleep during the ICU stay. The scale									
13	evaluates perceptions of sleep depth, sleep onset latency, number of awakenings, time spent									
14	awake, and overall sleep quality. The content validity of the Chinese version of the RCSQ									
15	questionnaire is 0.840, and the Cronbach's $\alpha$ coefficient is 0.874.									
16	PTSD									
17	The 17-item PTSD Checklist (PCL) correspond to the DSM-III-R symptoms of PTSD and serves									
18	as a self-report scale for assessing PTSD[28,29]. Patients will be asked to rate their agreement									
19	with each item on a scale from one (not at all) to five (extremely). PTSD-symptoms are									
20	categorized into re-experiencing (flashback, nightmare, emotional cue reactivity, and physical									
21	cue reactivity), avoidance and emotional numbing (avoidance of thoughts and reminders,									
22	amnesia, loss of interest, detachment, restricted affect, and foreshortened future), and									
23	hyperarousal (irritability/anger, sleep disturbance, difficulty concentrating, hypervigilance,									
24	exaggerated startle response). The total score ranges from 17 to 85[30].									
	13									

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) .

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

A previous study confirmed the good reliability and validity of the PCL, including testretest reliability of 0.96, internal consistency reliability of 0.94, and predictive validity of 0.64[31]. High correlations with the Symptom Checklist-90 further confirm its reliability and validity[32].

5 ICU memory

The ICU-Memory Tool (ICU-M) will be used to measure ICU patients' ICU experience[33]. This tool includes 14 questions (five open-ended questions and nine closed-ended questions), and is primarily divided into three parts: memories before admission to the ICU; memories during the ICU stay and memories after transferring out of the ICU. Memories during the ICU stay are categorized into three subscales: factual memories (lights, alarms, voices, families, faces, breathing tube, suctioning, darkness, clock, tube in your mouth, and wound care), memories of feelings (discomfort, confusion, sadness, anxiety/fear, panic, and pain), and memories of delusions (feeling that people were trying to hurt you, hallucinations, nightmares, dreams). The total number of memories in each of the three subscales will be summed. The Chinese version of ICU-M has a Cronbach's  $\alpha$  coefficient of 0.823 and a scale-level content validity index of 0.946, confirming its good reliability and validity[34]. Patients' clinical outcomes Medical outcomes will be extracted by the outcome assessor from the electronic health care system upon participants' discharge. This information includes: (a) ICU length of stay: the total number of days a patient stays in ICU; (b) 30-day mortality: the total death cases among all eligible cases at 30 days after admission to ICU; (c) duration of mechanical ventilation: the 

registered time in hours that the patients are on the mechanical ventilator; (d) the duration of use

of physical restraint: the recorded time in hours that the patients are receiving physical restraint;

(e) sedation use: the documented total amount and average doses (mg/ per day) of sedation by
using the conversion measurement of the same quantity of dexmedetomidine. (f) analgesics use:
the documented total amount and average doses (mg/ per day) of analgesics using the conversion
measurement of the same quantity of propofol. (g) self-extubation: the documented amount of
self-extubation cases; (h) ICU acquired infection: the documented amount of self-acquired

6 infection cases.

7 Quality of life

8 The EuroQol- 5 Dimension (EQ-5D) will be used to assess the participants' quality of life. It 9 assigns a grade on a scale ranging from 0 (representing the worst possible health status) to 100 10 (representing the best possible health status) based on one question for each of the five 11 dimensions, including mobility, self-care, usual activities, pain/discomfort, and BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

and data mining, AI training, and similar technologies

Protected by copyright, including for uses related to text

12 anxiety/depression[35].

13 Independence and cognitive function

FIM (Functional Independence Measure) will be used to measure both the independence and cognitive function. The FIM is comprised of 18 items, which are grouped into two subscales: motor and cognition. The motor items are adapted from the Barthel Index and are collectively known as the Motor-FIM. These items includes: Eating, Grooming, Bathing, Dressing (upper body), Dressing (lower body), Toileting, Bladder management, Bowel management, Transfers (bed/chair/wheelchair), Transfers (toilet), Transfers (bath/shower), Walk/wheelchair, and Stairs. The cognition subscale, known as the Cognitive-FIM, includes the following items: Comprehension, Expression, Social interaction, Problem solving, and Memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 to 7. A higher score 

23 indicates greater independence in performing the task associated with that item. The

#### 

1 Inter-Rater Reliability of FIM has been established with acceptable psychometric performance,

2 with Intraclass corelation coefficients ranging from 0.86 to 0.88. Concurrent validity with the

3 Barthel Index (ICC > 0.83) have demonstrated strong construct validity between items on

4 Barthel Index and items on the FIM the measure functional limitations [36].

5 Sociodemographic and clinical information

Sociodemographic and clinical information including ICU patients and family caregivers' age,
gender, educational level, marital status, occupation, the relationship between ICU patients and
family caregivers, and the health history of ICU patients will be collected.

9 Data collection

10Two research assistants, both trained consistently, will commence by explaining the11study and obtaining written informed consent from the participants. Subsequently, an ICU nurse12with a master's degree and a postgraduate student specializing in nursing will gather patients'13demographic data from their medical records and collect information on their quality of life,14independence, and cognitive function prior to admission to the ICU from the participants' family15caregivers. The nurses in charge of the study ICU will assess the CAM-ICU, RASS, RCSQ16during daily routine. On the fourteenth day of a patient's ICU hospitalization, or upon discharge17if the ICU stay is less than 14 days, the research assistant will collect data on secondary measures18(PTSD, ICU memory), clinical outcomes, independence, and cognitive function. Additionally,19quality of life, independence, and cognitive function will be assessed via a phone call by the20research assistant six months after the completion of the intervention. Notably,21Two research centers each have two research assistants dedicated to obtaining informed consent22and collecting data, respectively.

Page 17 of 26

### BMJ Open

1	Data management
2	Each patient has a case report form (CRF) for data collection, initially documented on paper.
3	Following this, the data from the CRFs are transferred to Excel spreadsheets on computers.
4	Access to the Excel files will be restricted through password protection. Only authorized
5	personnel participating in the study will have access to these files. All data entry and
6	manipulation activities will be logged and tracked to maintain transparency and accountability.
7	To identify and rectify errors, such as missing values, outliers, and typos, data cleaning strategies
8	will be employed[37]. Several methods will be employed to detect errors and minimise the
9	impacts on the accuracy of results. Firstly, the original dataset (in Excel) will be manually
10	checked to identify data error. Secondly, statistical graphical explorations including box plots,
11	histograms and scatter plots, along with descriptive statistics such as mean, frequency, and
12	percentage, will be used. Through this process, data errors, including typos, outliers, and
13	violations of integrity constraints, will be corrected.
14	Data analysis
15	This study will utilize R4.3.2 software for data analysis, with statistical analysis led by two
16	master's degree-holding research personnel. All statistical tests will be two-tailed, with the
17	significance level set at 0.05. To assess the normal distribution of continuous variables,
18	skewness, kurtosis, Q-Q plots, and histograms will be examined. Variables with skewness and
19	kurtosis values within the range of -2.0 to 2.0 will be considered to have a normal distribution.
20	For normally distributed continuous variables, the study will describe them using the mean $\pm$
21	standard deviation (Mean $\pm$ SD). For variables that do not meet the normal distribution criteria,
22	the study will describe them using the median (interquartile range, IQR). Categorical variables

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

continuous variables are met, independent two-sample t-tests will be used to compare differences between different groups. Otherwise, the Wilcoxon-Mann-Whitney will be employed. For categorical variables, chi-square tests and Fisher's exact tests will be used to compare differences between different groups. Additionally, missing values will be imputed using multiple imputation methods. The study will follow the intention-to-treat (ITT) and per-protocol (PP) principle for analysis. After imputing missing data using multiple imputation methods, the study will perform ITT and PP analysis and report relevant uncertainty indicators, such as confidence intervals and standard errors, in the results. This study will employ mixed-effects models for outcomes with repeated measurements. These models, also known as multilevel or hierarchical models, are effective for analyzing data with a hierarchical structure, such as repeated measurements. Fixed effects will estimate population-level relationships between predictors and outcomes. Our study will include predictors like APACHE-II score, age, admission category, and use of sedatives and analgesics as fixed explanatory variables. Subgroup analyses based on age, gender, and length of ICU stay will be conducted. 

### **DISCUSSION**

This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function). It employs a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention within ICUs, which enhances the reliability and validity of findings. The methodological rigor of this design provides valuable insights into the effectiveness of such interventions in clinical settings. Previously, our primary outcome included both the incidence 

Page 19 of 26

#### **BMJ** Open

duration and severity of delirium. However, considering the recommendation to focus on a single
primary outcome, we have designated delirium-free days as the primary outcome. Consequently,
we have classified delirium duration and severity as secondary outcomes, and this update has
been reflected in the trial registry.

In our study, our primary focus is on preventing delirium. However, if delirium does occur, physicians may prescribe antipsychotic medications. We will accurately document whether patients receive these medications and the dosage administered. Furthermore, we will maintain detailed records of the dosage of sedatives and analgesics administered to patients throughout the study. Additionally, in the intervention, family caregivers are involved through a "sample reorientation message," which refers to a written communication provided to help them understand and navigate changes in care, treatment, or environment. We acknowledge that family involvement may influence patient outcomes and could act as a confounding factor in our study. The observed effects may result from a combination of the VR intervention and changes in family behavior. Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) .

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

The study anticipates prompt availability of materials from family members and has contingency plans in place to ensure timely initiation of the VR intervention. However, delays in obtaining materials from family members may occur, potentially impacting the initiation of the VR intervention. Additionally, the use of antipsychotic medications to manage delirium may influence study outcomes, and while their administration will be documented, their effects on study outcomes may not be fully controlled.

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

2
3
4
5
c c
0
/
8
9
10
11
12
13
1/
14
15
16
17
18
19
20
21
22
22
20
24
25
26
27
28
29
30
31
32
22
27
34
35
36
37
38
39
40
41
42
<u>⊣∠</u> ∕\2
40 44
44
45
46
47
48
49
50
51
52
52 52
53
54
55
56
57
58
50

1

# 1 ETHICS AND DISSEMINATION

For patients in the Intensive Care Unit ICU, obtaining informed consent can be a complex 2 3 process due to the patients' health conditions. When possible, and when the patient is capable of understanding and making decisions, we will seek written consent directly from the patient. 4 However, for those who may be too ill to provide consent, we will obtain written consent from 5 their legally authorized representatives, typically family members. We are committed to ensuring 6 7 that all potential participants, or their designated representatives, are fully informed about the study's objectives and procedures. This includes providing detailed information about the study, 8 its potential risks and benefits, and the voluntary nature of participation. 9 We are dedicated to upholding the highest ethical standards in disseminating our research 10 findings. Study outcomes will be shared through peer-reviewed publications and presented at 11 academic conferences, ensuring that our work reaches the relevant professional and scientific 12 audiences. We are steadfast in our efforts to safeguard the rights and confidentiality of all 13 participants. To preserve individual privacy, all personal information will be anonymized, and 14 the findings will be communicated in a manner that protects the identities of the participants. 15 **Funding statement** 16 This study has received support from the China Postdoctoral Science Foundation 17 (2023M731551) and the Science and Technology Project of Shenzhen 18 19 (JCYJ20230807142300002). **Competing interests statement** 20 The authors declare that they have no competing interests. 21 22

23 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or disseminationplans of our research.

27 Contributors

26

60

### **BMJ** Open

# LSR, LY, WTX, LD, HMX, and TJF contributed to the study's conception and design. LSR led data management as the principal investigator, while HMX, WTX, and LY developed the study methods and provided supervision. All authors participated in drafting and revising the manuscript. LSR is the guarantor responsible for the integrity of the study. All authors approved the final manuscript and agreed to be accountable for the work. Word counts: 3997 Figure 1: Flowchart of VR-based sensory stimulation implementation OPP. References 1. Jayaswal AK, Sampath H, Soohinda G, Dutta S. Delirium in medical intensive care units: Incidence, subtypes, risk factors, and outcome. Indian J Psychiatry. 2019;61(4):352– 8. 2. Gravante F, Giannarelli D, Pucci A, Gagliardi AM, Mitello L, Montagna A, et al. Prevalence and risk factors of delirium in the intensive care unit: An observational study. Nurs Crit Care. 2021 May;26(3):156-65. 3. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FEJ, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr;291(14):1753-62. 4. Liang S, Chau JPC, Lo SHS, Bai L, Yao L, Choi KC. Validation of PREdiction of DELIRium in ICu patients (PRE-DELIRIC) among patients in intensive care units: A retrospective cohort study. Nursing in Critical Care. 2021 May;26(3):176-82.

Page 22 of 26

BMJ Open

1

2		
3 4	1	5. Mehta S, Cook D, Devlin JW, Skrobik Y, Meade M, Fergusson D, et al.
5 6	2	Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. Crit Care
7 8	3	Med. 2015 Mar;43(3):557-66.
9 10	4	6. Wolters AE, Peelen LM, Welling MC, Kok L, de Lange DW, Cremer OL, et al.
10	5	Long-Term Mental Health Problems After Delirium in the ICU. Crit Care Med. 2016
12	6	Oct;44(10):1808–13.
14 15	7	7. Liang S, Chau JPC, Lo SHS, Zhao J, Choi KC. Effects of nonpharmacological
16 17	8	delirium-prevention interventions on critically ill patients' clinical, psychological, and family
18 19	9	outcomes: A systematic review and meta-analysis. Australian Critical Care. 2021 Jul;34(4):378–
20 21	10	87.
22 23	11	8. Liang S, Chau JPC, Lo SHS, Choi KC, Bai L, Cai W. The effects of a sensory
24 25	12	stimulation intervention for preventing delirium in a surgical intensive care unit: A randomized
26 27	13	controlled trial. Nursing in Critical Care. 2023 Sep;28(5):709–17.
28 29	14	9. Liang S, Pak Chun Chau J, Hoi Shan Lo S, Chow Choi K, Bai L, Cai W. The
30 31	15	effects of a sensory stimulation intervention on psychosocial and clinical outcomes of critically
32 33	16	ill patients and their families: A randomised controlled trial. Intensive and Critical Care Nursing.
34 35	17	2023 Apr:75:103369
36 37	18	10 Strøm BS Vtrehus S Grov EK Sensory stimulation for persons with dementia: a
38 39	19	review of the literature I Clin Nurs 2016 Jul 25(13–14):1805–34
40 41	20	11 Moattari M Alizadeh Shirazi E Sharifi N Zareh N Effects of a Sensory
42 43	20	Stimulation by Nurses and Families on Level of Cognitive Function, and Basic Cognitive
44 45	21	Sensory Basevery of Comptees Detients With Severe Treumetic Drain Injury: A Dandomized
45 46 47	22	Centrel Triel Treams Mar. 2016 Sen:21(4):e22521
47 48	23	Control Irial. Irauma Mon. 2016 Sep;21(4):e23531.
49 50	24	12. Liang S, Chau JPC, Lo SHS, Zhao J, Liu W. Non-pharmacological delirium
51 52	25	prevention practices among critical care nurses: a qualitative study. BMC Nurs. 2022 Aug
53 54	26	25;21(1):235.
55 56		
57 58		22
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Page 23 of 26

#### **BMJ** Open

2		
3 4	1	13. Liang S, Chau JPC, Lo SHS, Li S, Gao M. Implementation of ABCDEF care
5 6	2	bundle in intensive care units: A cross-sectional survey. Nursing in Critical Care. 2021
7 8	3	Sep;26(5):386–96.
9 10	4	14. Luan L, Ding M. Progress in the application of virtual reality technology in
11 12	5	critically ill patients in ICU. Chinese Journal of Nursing. 2021 Aug 15;56(8):1255.
13 14	6	15. Jawed YT, Golovyan D, Lopez D, Khan SH, Wang S, Freund C, et al. Feasibility
15 16	7	of a virtual reality intervention in the intensive care unit. Heart Lung. 2021;50(6):748-53.
10 17 18	8	16. Ong TL. The DREAMS Project: Improving the Intensive Care Patient Experience
19 20	9	with Virtual Reality [Internet]. [cited 2023 Oct 13]. Available from:
20 21 22	10	https://arxiv.org/abs/1906.11706
22 23 24	11	17. Ong TL, Ruppert MM, Akbar M, Rashidi P, Ozrazgat-Baslanti T, Bihorac A, et
25 26	12	al. Improving the Intensive Care Patient Experience With Virtual Reality-A Feasibility Study.
27 28	13	Crit Care Explor. 2020 Jun;2(6):e0122.
20 29 30	14	18. Restorative effects of virtual nature settings - PubMed [Internet]. [cited 2023 Oct
31 32	15	13]. Available from: https://pubmed.ncbi.nlm.nih.gov/20950174/
33 34	16	19. Ohly H, White MP, Wheeler BW, Bethel A, Ukoumunne OC, Nikolaou V, et al.
35 36	17	Attention Restoration Theory: A systematic review of the attention restoration potential of
37 38	18	exposure to natural environments. J Toxicol Environ Health B Crit Rev. 2016;19(7):305-43.
39 40	19	20. Chirico A, Cipresso P, Yaden DB, Biassoni F, Riva G, Gaggioli A. Effectiveness
40 41 42	20	of Immersive Videos in Inducing Awe: An Experimental Study. Sci Rep. 2017 Apr
43 44	21	27;7(1):1218.
45 46	22	21. Toyabe S ichi, Kouhei A. Referral from secondary care and to aftercare in a
40 47 48	23	tertiary care university hospital in Japan. BMC Health Services Research. 2006;6(1):11.
40 49 50	24	22. Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S, et al.
50 51 52	25	Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond
52 53 54	26	Agitation-Sedation Scale (RASS). JAMA. 2003 Jun;289(22):2983-91.
55 56		
50 57 59		23
58 59		

Page 24 of 26

BMJ Open: first published as 10.1136/bmjopen-2024-083966 on 15 January 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

# BMJ Open

2 3	1	23. Moon K, Lee S. The effects of a tailored intensive care unit delirium prevention
4 5	2	protocol: A randomized controlled trial. International journal of nursing studies.
6 7	3	2015;52(9):1423–32.
8 9	4	24. Mailhot T, Cossette S, Côté J, Bourbonnais A, Côté MC, Lamarche Y, et al. A
10 11	5	post cardiac surgery intervention to manage delirium involving families: a randomized pilot
12 13	6	study. Nursing in critical care. 2017 Jul;22(4):221–8.
14 15	7	25. Munro C, Cairns P, Ji M, Calero K, Anderson W, Liang Z. Delirium prevention in
16 17	8	critically ill adults through an automated reorientation intervention – A pilot randomized
18 19	9	controlled trial. Heart & Lung - The Journal of Acute and Critical Care. 2017;46(4):234–8.
20 21	10	26. Zou J. Reliability and validity test of Chinese version of CAM-ICU and
22 23	11	comparison with other scales. Huazhong University of Science and Technology; 2012.
24 25	12	27. Babar A. Khan, Perkins Anthony J, Sujuan Gao, Siu L. Hui, Campbell L. Noll,
26 27	13	Farber Mark O, Chlan Linda L BMA, Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, et al.
28 29	14	The CAM-ICU-7 Delirium Severity Scale: A novel delirium severity instrument for use in the
30 31	15	Intensive Care Unit. Critical care medicine. 2017;45(5):851–7.
32 33	16	28. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist
34 35	17	(PCL): Reliability, Validity, and Diagnostic Utility. New York: Guilford Press; 1993.
36 37	18	29. Mollica RF, Caspi-yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard
38 39	19	trauma questionnaire: Validating a cross-cultural instrument for measuring torture, trauma, and
40 41	20	posttraumatic stress disorder in indochinese refugees. The journal of nervous and mental disease.
42 43	21	1992;180(2):111-6.
44 45	22	30. Svenningsen H, Egerod I, Christensen D, Tonnesen EK, Frydenberg M, Videbech
46 47	23	P. Symptoms of posttraumatic stress after intensive care delirium. BioMed Research
48 49	24	International. 2015;
50 51	25	31. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric
52 53	26	properties of the PTSD checklist (PCL). Behaviour research and therapy. 1996;34(8):669-73.
54 55		
50 57 59		24
50 59 60		For peer review only - http://bmiopen.bmi.com/site/about/quidelines.xhtml
00		

Page 25 of 26

# BMJ Open

1 2			
3 4	1	32. Yang L, Yang X, Yang H, Liu Q. Study on the validity, reliability and influencing	
5 6	2	factors of the civilian version of the Post-traumatic Stress Checklist. Chinese Journal of Health	
7 8	3	Psychology. 2007;15(1):6–9.	
9 10	4	33. Jones C, Humphris G, Griffiths RD. Preliminary validation of the ICUM tool: a	
11 12	5	tool for assessing memory of the intensive care experience. Clinical Intensive Care.	
13 14	6	2000;11(5):251–5.	
15 16	7	34. Huang L, Jiang Q, Lin X, Hou W, Wang S, Wang X. The reliability and validity	
10 17 19	8	test of ICU Memory Scale. Chinese Journal of Nursing. 2016;51(10):1265–9.	
10 19 20	9	35. Balestroni G, Bertolotti G. [EuroQol-5D (EQ-5D): an instrument for measuring	
20 21 22	10	quality of life]. Monaldi Arch Chest Dis. 2012 Sep;78(3):155–9.	
22	11	36. Parallel reliability of the functional independence measure and the Barthel ADL	
24 25 26	12	index - PubMed [Internet]. [cited 2023 Oct 13]. Available from:	
20 27 28	13	https://pubmed.ncbi.nlm.nih.gov/11117590/	
20 29 20	14	37. Van Den Broeck J, Cunningham SA, Eeckels R, Herbst K. Data cleaning:	
30 31	15	Detecting, diagnosing, and editing data abnormalities. PLoS medicine. 2005;2(10):966-70.	
32 33			
34 35	16		
36 37			
38 39			
40 41			
42 43			
44 45			
46 47			
48 49			
50 51			
52 53			
54 55			
56 57		25	
58 59		25	
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

