Virtual Reality Intervention for Post-Intensive Care Syndrome (PICS): A Protocol for a Pilot Randomized Controlled Trial for Cognitive, Physical and Psychological Outcomes

Protocol Identification

Item	Content
Brief Title	Virtual Reality for Recovery After Intensive Care (PICS)
Protocol Date	6 December 2025
Ethics Approval	CE-319-22 by Ethics Committee of CHUSJ
Funding	FCT - Foundation for Science and Technology (Grant 2022.13901.BDANA and Support UID/50014/2025 (https://doi.org/10.54499/UID/50014/2025))

1. Introduction

1.1. Background and Rationale

Post-intensive care syndrome (PICS) is a prevalent and debilitating condition affecting up to 50–75% of ICU survivors [1,2]. It encompasses physical, cognitive, and psychological impairments, all of which substantially reduce patients' quality of life [2]. Delirium, a hallmark cognitive impairment in PICS, affects 50–80% of ICU patients [3], while approximately one-third develop psychological sequelae such as anxiety, depression, or post-traumatic stress disorder (PTSD) [4,5]. These long-term complications can persist for months or years after discharge, limiting independence and hindering return to prior daily activities [4].

The ICU environment itself contributes substantially to the development of PICS. Patients are exposed to stress-inducing factors including sensory overload, sensory deprivation, isolation, disrupted circadian rhythms, and lack of temporal orientation or control [2]. Prolonged immobility and sedation exacerbate physical impairments such as ICU-acquired weakness, while psychological stressors increase vulnerability to anxiety, depression, and PTSD [1,2,6,7]. Importantly, many PICS-related impairments arise not from the underlying illness but from ICU-related factors, highlighting the need for early, targeted interventions [1].

Current rehabilitation strategies in ICUs are often limited by time, resource, and feasibility constraints, and rarely address the multifaceted nature of PICS in a holistic manner [1,8]. Novel interventions capable of simultaneously targeting cognitive, physical, and psychological domains while being feasible in critical care settings are urgently needed.

1.2. Rationale for Virtual Reality (VR) Intervention

Virtual reality (VR) has emerged as a promising tool to meet the multi-domain rehabilitation needs of ICU patients. VR systems, using head-mounted displays (HMDs), create immersive environments that transport patients out of the stressful ICU setting into calming, engaging virtual spaces [2].

- **Mechanism of Action:** These environments allow for the delivery of tailored therapeutic activities, including physical and cognitive exercises, even for patients with limited mobility [9]. Evidence suggests that VR can enhance motor and cognitive recovery, reduce psychological distress, and improve patient engagement through safe, controlled, and enjoyable experiences [3,9]. VR's immersive quality also allows it to potentially aid patients in processing traumatic or delusional memories, thereby addressing psychological contributors to PICS [1,5].
- **Scientific Gap:** Despite the promising outcomes of early rehabilitation and immersive technology, evidence for an **early, effective, multi-domain intervention** in the acute ICU setting remains limited [1]. Previous studies often fail to definitively disentangle the effects of immersive VR technology from the therapeutic content itself, or from novelty effects [1,5,8].
- **Justification for Trial Design:** To rigorously evaluate the added value of immersive VR technology over content alone, we will conduct a pilot randomized controlled trial. Participants will be allocated to one of three parallel groups:
    a. VR-based rehabilitation (VR-Rehab)
    b. Tablet-based rehabilitation with identical content (Tablet-Rehab)
    c. Standard of Care (SOC)

By comparing these three groups, we can differentiate between the impact of structured digital stimulation (Tablet) and the psychological/physiological impact of total immersion (VR) relative to traditional bedside care.

1.3. Objectives and Hypotheses

The primary objective of this trial is to evaluate the feasibility and preliminary efficacy of a 3-arm ICU rehabilitation protocol and to isolate the effect of immersive VR technology on cognitive function. By comparing VR-Rehab to both Tablet-Rehab (same content) and Standard of Care (SOC), the study aims to isolate the therapeutic contribution of "immersion" versus "digital content" alone.

While cognitive recovery is the primary focus, the study includes several secondary objectives:

- **Multi-Domain Recovery:** To explore effects on physical (MRC Sum-score) and psychological (IES-R) health.
- **Protocol Adherence:** To evaluate the "minimum therapeutic dose" by comparing the Intent-to-Treat (all participants) and Per-Protocol (min. sessions met) populations.

- **Feasibility & Safety:** To monitor recruitment barriers, session completion, and adverse events like cybersickness in the ICU.

The research questions focus on whether immersive VR leads to superior cognitive improvements compared to tablet-based and standard care, and to what extent the immersion factor provides additional benefits to physical and psychological recovery. We also ask what relationship exists between the "dose" of VR received and the magnitude of recovery.

We hypothesize a "step-wise" effect where VR-Rehab outperforms Tablet-Rehab, which in turn outperforms SOC, supporting the "Immersion Hypothesis." We further hypothesize that a measurable dose-response effect will be observed in participants who meet the minimum protocol conditions, despite the high-acuity barriers of the ICU.

1.4. Expected Significance and Contribution to Clinical Practice

This study addresses a critical gap in critical care by attempting to disentangle the therapeutic effects of immersive technology from digital content alone. By utilizing a three-arm randomized design, the findings will provide a unique proof-of-concept for the added value of immersion in treating the multi-domain impairments of PICS.

- **Scientific Contribution:** The trial will clarify whether the neurological engagement of VR offers a superior "immersion effect" for cognitive and psychological recovery compared to traditional tablet-based exercises. Furthermore, by analyzing both Intent-to-Treat and Per-Protocol data, this research will contribute to defining the "minimum effective dose" of digital rehabilitation required to elicit clinical change in ICU survivors.
- **Clinical Contribution and Guideline Development:** Beyond statistical outcomes, a primary goal of this research is the development of evidence-based clinical guidelines for the use of VR in and post-ICU rehabilitation.

Ultimately, this study aims to provide clinicians with a practical framework to determine if the investment in VR hardware provides a significant enough recovery advantage to justify its implementation over simpler, tablet-based alternatives.

2. Methods and Study Design

2.1. Trial Design and Setting

This is a prospective, three-arm, parallel-group, randomized controlled pilot trial conducted at the ICU of Centro Hospitalar Universitário São João (CHUSJ). Recruitment began on November 4, 2025, with final recruitment closing on March 31, 2026, and follow-ups concluding on June 6, 2026. The study utilizes a 1:1:1 allocation ratio (VR-Rehab, Tablet-Rehab, and SOC) generated via R software.

2.2. Participant Eligibility Criteria

2.2.1 Inclusion Criteria

To ensure the population is capable of engaging with the digital interfaces while representing the typical PICS risk profile, patients must meet the following:

- Adult patients, 18 years or older
- Patients who received mechanical ventilation are prioritized, but non-ventilated patients are also eligible
- Ventilated patients must be in the post-extubation period
- The patient has a projected remaining hospital stay of at least 4 days (assessed by the clinical team)
- The patient has RASS score between -1 and +1
- The patient has the ability to move both arms, even if with difficulties, as assessed by the clinical team, to be able to interact with the software
- The patient can maintain a stable sitting position (30° to 60°)
- The patient is able to communicate (speech, gesturing, or writing)
- The patient can communicate and understand Portuguese
- The patient or a legal representative provided informed consent

2.2.2 Exclusion Criteria

To isolate the effect of the VR intervention and prevent confounding data, the following are excluded:

- Severe cognitive and neurodegenerative diseases: mental illness requiring institutionalization; acquired or congenital intellectual disability; known severe brain injuries (e.g., stroke with significant residual deficits); moderate to severe Traumatic Brain Injury (TBI) (defined by the duration of loss of consciousness/post-traumatic amnesia or documented residual deficits); diagnosed neurodegenerative diseases (e.g., Parkinson's disease with severe movement impairment, Huntington's disease, severe Alzheimer's disease, or dementia of any etiology that prevents autonomy in daily life at baseline)
- The patient uses neuromuscular blocking agents
- The patient has a positive CAM-ICU result at the time of initial screening
- The patient has active psychotic disorders or suicidal ideation
- The patient has documented epilepsy or history of seizures
- The patient has a "Do Not Resuscitate" (DNR) order, is on life support with exclusive focus on comfort, or has an unexpected survival predicted to be less than 24 hours
- The patient has intoxication by an active substance or withdrawal syndrome requiring ongoing medical management that prevents safe and meaningful participation or accurate cognitive assessment
- Patients with immobility or severe motor limitations in the upper limbs, fine motor skills, or cervical region

- The patient has open wounds on the head or face that may affect the comfortable/safe use of VR glasses, cause discomfort, or present a hygiene risk
- The patient has uncorrected blindness or deafness that prevents the safe/effective use of VR/tablet devices.
- Patients are participating in another rehabilitation study with interventions
- Patients with a scheduled surgery where the ICU stay is expected to be less than 24 hours

2.3. Informed Consent

Patients are screened by researchers and ICU staff for eligibility. Potential participants meeting all eligibility criteria are approached for consent and to discuss the study goals and procedures (Appendix 1). In cases where the patient is not yet capable of providing independent consent, informed consent is sought from a Legally Authorized Representative (LAR) or a family member.

The consent process initiates with verbal consent, followed by the signing of the formal informed consent document. If the patient is physically unable to sign the document, the LAR, a family member, or an impartial witness, such as a bedside nurse, can sign on their behalf.

A critical component of this trial's ethical framework is the requirement for daily re-consent. Before every intervention session or assessment, researchers verify the participant's willingness to continue. If a participant expresses a desire to discontinue their involvement entirely, they are recorded as a study loss, and the specific reason for withdrawal is recorded. If a participant expresses a desire to discontinue their involvement entirely, they are recorded as a study loss, along with the specific reason for withdrawal. Reasons for loss can be death, transfer, discharge, discontinuation (for clinically significant worsening of health status), withdrawal of consent, or loss to follow-up.

2.4. Safety and Mandatory Stop Criteria

The research team continuously monitors patient safety throughout the intervention. The session ends if the patient's physiological stability is lost (oxygen saturation (SpO_2) < 90%, heart rate (HR) change > 20%) or if the patient asks to stop treatment. Any verbal or non-verbal sign of discomfort, distress, or a direct request to stop results in the immediate removal of the device. All such interruptions are meticulously documented in the session logs (Appendix 2).

2.5. Data Management

All participant data is handled in strict compliance with the General Data Protection Regulation (GDPR). Each participant is assigned a unique Study ID (e.g., P-001) to ensure pseudonymization across all tracking documents. The master link between these IDs and the

patient hospital IDs is stored on a secure platform, accessible only to the primary research team.

Data is recorded across four distinct tabs from restricted Google Sheets: the Master Patient Log (Appendix 3) for demographics and clinical history, Level Metrics (Appendix 4) for specific game performance, Game Metrics (Appendix 5) for qualitative motor observations (e.g., tremors, symmetry), and Session Logs (Appendix 6) for physiological monitoring and interruption codes. Records will be retained for five to seven years post-publication before secure destruction.

2.6. Bias Mitigation

To maintain methodological rigor in a non-blinded trial, a strict separation of duties is enforced. Researchers facilitating the intervention sessions are prohibited from recording the primary outcome assessments (MoCA and MRC Sum-Score) or the in-game metrics on the same data sheets. This ensures that the delivery of the technology does not influence the scoring of recovery.

Furthermore, the primary analysis is performed using a pre-developed, automated script in the R software. By utilizing a "hands-off" algorithmic approach for group comparisons, the potential for subjective interpretation or manual data manipulation is eliminated. All researchers have declared no financial or non-financial conflicts of interest regarding the software provider (Virtuleap), and any previous contact with participants is disclosed to ensure transparency in the reporting of findings.

2.7. Sample Size Calculation

Given the exploratory nature of this pilot trial, the sample size was determined using the "Rule of Thumb" from Julious, 2005, for pilot studies, which suggests a minimum of 12 participants per arm to estimate the parameters required for future definitive trials [10].

To account for the high rates of attrition inherent in the post-ICU population, specifically losses due to hospital transfers, patient withdrawal, or failure to establish contact during the follow-up period, we estimated a 30% loss to follow-up. Consequently, the study established a recruitment target of 51 participants (17 per group).

2.8. Ethics and Sanitization

This study is conducted in strict accordance with the Declaration of Helsinki and the Oviedo Convention. Ethical approval was obtained from the Ethics Committee of the Centro Hospitalar Universitário de São João (CHUSJ) (Reference: [Insert Number]). The trial is registered at ClinicalTrials.gov (Identifier: [Number]).

To prevent cross-contamination, the Meta Quest Pro and Tablet are sanitized before and after every use using medical-grade, non-corrosive disinfectant wipes.

3. Study Interventions

All interventions are designed to be performed daily for a period of 7 days (or until discharge), with a target "dose" of 12 minutes per session. The sessions are conducted at the bedside, with patients positioned at an angle of 30° to 60° to ensure safety and comfort.

3.1. Standard of Care (SOC)

The control group receives the conventional rehabilitation protocol provided by the CHUSJ ICU clinical team. This typically includes passive or active range-of-motion exercises, respiratory physiotherapy, and early mobilization as dictated by the patient's clinical status. No structured digital cognitive training is provided. Interactions are limited to standard nursing care, family visits, and routine clinical assessments.

3.2. VR-Rehab + Standard of Care (VR-R)

Participants in this arm use the Meta Quest Pro head-mounted display to access the Enhance VR platform (Virtuleap) [11] for cognitive and motor tasks, administered in addition to SOC. Patients interact with the virtual environment using the controllers from the HMD. The intervention lasts a maximum of 7 days (7 sessions), with the possibility of playing a total of 42 games (6 per day). Table 1 details the specific game content and the standardized session duration.

Table 1. The selected EnhanceVR games, their corresponding targets, and gameplay duration.

VR Game Name	Cognitive/Physical Domain	Training Duration (min)
Assembly	Information Processing	2.00
Odd Egg	Problem Solving	2.50
Whack-a-Mole	Attention/Psychomotor Vigilance	1.50
Balance	Motor Control/Proprioception	2.50
Memory Wall	Working Memory/Recall	2.00
Slinger	Motor Dexterity	1.50
	Total Game Play	12.00

3.3. Tablet-Rehab + Standard of Care (T-R)

To isolate the effect of immersion, this group performs the same cognitive exercises as the VR group but via a 2D tablet interface (Samsung Galaxy S5e). These games were commercially available on the Google Play Store. As the VR-R group, the intervention lasts a maximum of 7 days (7 sessions), with the possibility of playing a total of 42 games (6 per day). Table 2 details the specific game content and the standardized session duration.

Table 2. The selected tablet games, along with their corresponding targets and gameplay durations.

Tablet Game Name	Cognitive/Physical Domain	Training Duration (min)
Ball Sorting [12]	Information Processing	2.00
Find the Difference [13]	Problem Solving	2.50
Whack-a-Mole [14]	Attention/Psychomotor Vigilance	1.50
Teeter Pro - Maze [15]	Motor Control/Proprioception	2.50
Memory Matrix [16]	Working Memory/Recall	2.00
Slingshot [17]	Motor Dexterity	1.50
	Total Game Play	12.00

4. Data Collection and Outcome Measures

4.1. Timepoints of Assessment

Data collection is divided into five distinct timepoints, spanning from the acute ICU phase to the post-discharge recovery phase:

- **T0 (Baseline):** At the time of enrollment (Day 0). Includes:
  - Cognitive: Montreal Cognitive Assessment (MoCA)
  - Physical: Medical Research Council Sum Score (MRC-SS) assessments.
  - Psychological: Visual Analogical Scale (VAS)
- **Daily during interventions:**
  - Psychological: Visual Analogical Scale (VAS)
  - VR-R: Simulator Sickness Questionnaire (SSQ)
- **T1 (Day 8 to 14):** From the day after the last intervention to the day before T2. Includes:
  - Psychological: Visual Analogical Scale (VAS)
  - VR-R and T-R: System Usability Scale (SUS)
- **T2 (Day 15 to 22):** From 1 to 2 weeks from the last intervention day. Includes:
  - Cognitive: Montreal Cognitive Assessment (MoCA)
  - Physical: Medical Research Council Sum Score (MRC-SS) assessments.
  - Psychological: Visual Analogical Scale (VAS); The Impact of Event Scale – Revised (IES-R); EQ-5D-5L Index health-related quality of life
- **T3 (Follow-up):** From 30 to 45 days after hospital discharge. Includes:
  - Cognitive: Montreal Cognitive Assessment (MoCA)
  - Physical: Medical Research Council Sum Score (MRC-SS) assessments.
  - Psychological: Visual Analogical Scale (VAS); The Impact of Event Scale – Revised (IES-R); EQ-5D-5L Index; Patient Health Questionnaire-9 (PHQ-9); General Anxiety Disorder-7 (GAD-7)
- **T4 (Follow-up):** From 3 to 6 months after hospital discharge. Includes:

- Cognitive: Montreal Cognitive Assessment (MoCA)
- Physical: Medical Research Council Sum Score (MRC-SS) assessments.
- Psychological: Visual Analogical Scale (VAS); The Impact of Event Scale – Revised (IES-R); EQ-5D-5L Index; Patient Health Questionnaire-9 (PHQ-9); General Anxiety Disorder-7 (GAD-7)

The Primary Outcome is Cognitive Function (MoCA). Secondary Outcomes include Physical (MRC Sum Score), Psychological/Trauma (IES-R), Psychological Distress (PHQ-9, GAD-7), and Quality of Life (EQ-5D-5L). Daily VAS scores and CAM-ICU results are recorded to monitor clinical trajectory.

Since some timepoint assessments could be over the phone (T1-T4), the blinded version of MoCA and self-reported MRC-SS (Appendix 7) would be used.

4.2. Minimum Therapeutic Dose

The "Minimum Therapeutic Dose" is a crucial threshold for the Per-Protocol (PP) analysis. It is defined as the successful completion of at least 12 individual games over the course of the 7-day-week intervention period. This metric ensures that the patient has reached a sufficient level of digital immersion and cognitive engagement to reasonably evaluate the impact of the technology on recovery.

4.3. Data Retrieval and Outcome Measures

Data is categorized into three primary streams to provide a holistic view of the patient's progress: Clinical Characterization and Baseline Data, In-Metric Data (Level and Game layers), and Observational and Physiological Data.

4.3.1 Clinical Characterization and Baseline Data

To ensure a comprehensive profile of each participant and provide necessary covariates for the statistical analysis, extensive clinical and demographic data are abstracted from the electronic medical records. This data is recorded in the Master Patient Log (Appendix 3) and includes identifiers (Study ID, Hospital ID), randomization details, and demographic markers (Age, Gender, Education).

Clinical acuity is captured via APACHE II and SOFA scores, alongside detailed records of ICU interventions such as the duration of invasive mechanical ventilation, incidence and duration of delirium (CAM-ICU), and total days of sedation and analgesia. Additionally, the log tracks the total length of stay (ICU and Hospital) and specific participation metrics, including the final status and reasons for any loss to follow-up.

4.3.2 In-Metric Data

For participants in the VR-Rehab (VR-R) and Tablet-Rehab (T-R) arms, performance data is extracted from gameplay screen recordings. This objective data is categorized into two granular layers:

- **Level Metrics (Appendix 4):** Captures "micro-metrics" for every round played, including level duration, score, and a detailed error analysis (omission, commission, and sequence errors). It also tracks temporal precision through average resolution and reaction times.
- **Game Metrics (Appendix 5):** Provides a "macro" summary of the session, including total scores and levels completed. Crucially, this log incorporates researcher-led motor observations, documenting movement smoothness, tremors, bimanual coordination, symmetry, and head-hand alignment to assess physical-cognitive integration.

4.3.3 Observational and Physiological Data

This "macro" dataset tracks the patient's physiological state and the overall feasibility of the 12-minute intervention. As detailed in Appendix 6, variables include:

- **Physiological Monitoring:** Pre-, intra-, and post-monitoring of heart rate, SpO2, arterial pressure, and body temperature.
- **Patient-Reported Metrics:** Fatigue levels via the Borg CR10 Scale (pre/post), patient engagement levels, and the Visual Analogue Scale (VAS) for daily wellness.
- **Operational Feasibility:** Detailed tracking of setup time, supervisor involvement, and total session duration, including the frequency and rationale for any pauses.
- **Clinical Safety:** Daily CAM-ICU results, documentation of adverse events, and "Voided Session" codes to identify barriers to protocol adherence.

4.3. Statistical Methods

4.3.1. General Principles

The primary analysis will follow the **Intention-to-Treat (ITT)** principle, including all randomized participants. A **Per-Protocol (PP)** sensitivity analysis will be conducted, restricted to participants who reached the **Minimum Therapeutic Dose** (completion of a minimum of 12 games and the assessments from T0 to T2). All statistical tests will be two-sided, with significance set at $\alpha = 0.05$. Effect sizes (Hedges' g) and 95% Confidence Intervals will be reported for all outcomes to assess clinical relevance and facilitate future power calculations.

4.3.2. Handling of Missing Data

Missing data at follow-up (T3, T4) will be addressed using **Multiple Imputation by Chained Equations (MICE)**. The imputation model will incorporate APACHE II scores, baseline MoCA, and duration of mechanical ventilation. To account for the protocol transition after participant P7 (change from 2 sessions/day to 1 session/day), "Protocol Version" will be included as a covariate in sensitivity analyses to ensure that delivery frequency does not bias the estimation of the intervention effect.

4.3.3. Clinical Outcomes Analysis

Each domain will be analyzed independently to identify specific areas of clinical improvement. A **Linear Mixed-Effects Model (LMEM)** will be fitted for each outcome (MoCA, MRC-SS, etc.) to handle the longitudinal nature of the data and missing observations.

- **Fixed Effects:** Group (VR-Rehab, Tablet-Rehab, SOC), Time Point, and the Group * Time interaction.
- **Random Effects:** Random intercept for Subject ID to account for individual baseline variance.
- **Covariates:** Models will be adjusted for **APACHE II** score and **Duration of Invasive MV** (hours).

4.3.4. In-Game Performance & Learning Curves (Process Metrics)

Gameplay metrics will be analyzed for the VR and Tablet groups to evaluate the impact of immersive technology:

- **Cognitive-Motor Efficiency:** A "Throughput" metric (Correct Responses per Minute) will normalize performance across different game durations.
- **Learning Curves:** Session-to-session progression will be modeled using LMEM, with Session Number treated as a continuous variable.
- **Motor Quality:** Game-specific metrics (Smoothness, Tremors, Bimanual Coordination) will be compared between digital groups using **Mann-Whitney U tests** or **t-tests**, depending on data distribution.

4.3.5. Safety, Feasibility, and Physiological Response

- **Safety:** Incidence of Adverse Events (AEs) and SSQ scores will be reported descriptively.
- **Exertion:** The change in **Borg CR10** (post–pre) will be analyzed to compare the "fatigue cost" of the two digital interventions.
- **Physiological Response:** Median Heart Rate, SpO_2, and Arterial Pressure will be analyzed descriptively. For participants with continuous monitoring, the **Area Under the Curve (AUC)** for Heart Rate will be compared to assess autonomic arousal.
- **Usability:** System Usability Scale (SUS) scores will be compared between VR and tablet groups at T1.

5. References

1. Ong, T.L., Ruppert, M.M., Akbar, M., Rashidi, P., Ozrazgat-Baslanti, T., Bihorac, A., Suvajdzic, M., 2020. Improving the intensive care patient experience with virtual reality—a feasibility study. Crit. Care Explor. 2, e0122. https://doi.org/10.1097/cce.0000000000000122.
2. Gerber, S.M., Jeitziner, M., Knobel, S.E.J., Mosimann, U.P., Müri, R.M., Jakob, S.M., Nef, T., 2019. Perception and performance on a virtual reality cognitive stimulation for use in the intensive care unit: a non-randomized trial in critically ill patients. Front. Med. 6, 287. https://doi.org/10.3389/fmed.2019.00287.
3. Suvajdzic, M., Bihorac, A., Rashidi, P., Ruppert, M., Williams, S., Ozrazgat-Baslanti, T., Ong, T., Appelbaum, J., 2019. Developing a patient-centered virtual reality healthcare system to prevent the onset of delirium in ICU patients, in: 2019 IEEE 7th International Conference on Serious Games and Applications for Health (SeGAH). IEEE, pp. 1–8. https://doi.org/10.1109/segah.2019.8882442.
4. Vlake, J.H., Van Bommel, J., Wils, E., Bienvenu, J., Hellemons, M.E., Korevaar, T.I., Schut, A.F., Labout, J.A., Schreuder, L.L., Van Bavel, M.P., Gommers, D., Van Genderen, M.E., 2022. Intensive care unit–specific virtual reality for critically ill patients with COVID-19: multicenter randomized controlled trial. J. Med. Internet Res. 24, e32368. https://doi.org/10.2196/32368.
5. Vlake, J.H., Van Bommel, J., Hellemons, M.E., Wils, E., Gommers, D., Van Genderen, M.E., 2021. Intensive care unit-specific virtual reality for psychological recovery after ICU treatment for COVID-19: a brief case report. Front. Med. 7, 629086. https://doi.org/10.3389/fmed.2020.629086.
6. Rousseaux, F., Dardenne, N., Massion, P.B., Ledoux, D., Bicego, A., Donneau, A., Faymonville, M., Nyssen, A., Vanhaudenhuyse, A., 2021. Virtual reality and hypnosis for anxiety and pain management in intensive care units. Eur. J. Anaesthesiol. 39, 58–66. https://doi.org/10.1097/eja.0000000000001633.
7. Badke, C.M., Krogh-Jespersen, S., Flynn, R.M., Shukla, A., Essner, B.S., Malakooti, M.R., 2022. Virtual reality in the pediatric intensive care unit: patient emotional and physiologic responses. Front. Digit. Health 4, 867961. https://doi.org/10.3389/fdgth.2022.867961.

8. Locke, B.W., Tsai, T., Reategui-Rivera, C.M., Gabriel, A.S., Smiley, A., Finkelstein, J., 2024. Immersive virtual reality use in medical intensive care: mixed methods feasibility study. JMIR Serious Games 12, e62842. https://doi.org/10.2196/62842.
9. Lai, B., Powell, M., Clement, A.G., Davis, D., Swanson-Kimani, E., Hayes, L., 2021. Examining the feasibility of early mobilization with virtual reality gaming using head-mounted display and adaptive software with adolescents in the pediatric intensive care unit: case report. JMIR Rehabil. Assist. Technol. 8, e28210. https://doi.org/10.2196/28210.
10. Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics, 4(4), 287–291. https://doi.org/10.1002/pst.185
11. EnhanceVR Games - Unlock your potential with the perfect training. (n.d.). Virtuleap. Retrieved September 17, 2025, from https://virtuleap.com/enhance
12. Ball Sort Puzzle - Color Game - apps on Google Play. (n.d.). https://play.google.com/store/apps/details?id=ball.sort.puzzle.color.sorting.bubble.games
13. Encontre diferenças Jogos - Apps on Google Play. (n.d.). https://play.google.com/store/apps/details?id=puzzle.game.find.differences
14. Whack a Mole: Tap it!- Apps on Google Play. (n.d.). https://play.google.com/store/apps/details?id=com.lcyu.whackamole
15. Teeter Pro - labyrinth maze - Apps on Google Play. (n.d.). https://play.google.com/store/apps/details?id=pl.surix.teeterpro
16. Memory Matrix - apps on Google Play. (n.d.). https://play.google.com/store/apps/details?id=com.T0pCode.Memory.Matrix
17. Slingshot Championship - apps on Google Play. (n.d.). https://play.google.com/store/search?q=slingshot+championship&c=apps

Appendix 1

INFORMED CONSENT

Research Project: Cognitive, Physical and Psychological Rehabilitation with Virtual Reality in Intensive Care Survivors

You are being invited to participate in a research project. This document contains information about the research study being conducted at the São João Hospital. The research aims to find new ways to help the recovery of people who have been admitted to the Intensive Care Unit (ICU). Before deciding whether you wish to participate, it is important that you understand why the research is being carried out and what participation will involve. Please take some time to read this document carefully. Ask us if there is anything that is not clear or if you would like further information.

What is the purpose of the study?

The study aims to find new ways to help the recovery of people who have been admitted to the Intensive Care Unit (ICU).

Is participation voluntary?

Yes. Participation in this study is entirely voluntary. You may decide not to participate or, if you agree to participate, you may withdraw at any time without needing to provide a reason. Your decision will not in any way affect the healthcare you receive or will receive.

What does participation in the study involve?

Participation in the study has three phases:

1. Randomization

If you agree to participate, you will be randomly assigned to one of three groups:

- **Group 1:** Receives the usual care and rehabilitation exercises.
- **Group 2:** In addition to usual care, performs extra exercises using a tablet.
- **Group 3:** In addition to usual care, performs extra exercises using virtual reality glasses/headset.

2. Intervention and Assessments (During Hospitalisation)

This phase lasts a maximum of 7 days while you are in hospital. If you belong to Groups 2 or 3 (Tablet or VR):

- You will complete extra exercise sessions lasting approximately 20 to 30 minutes.
- The exercises are performed in bed, always with a researcher and a nurse present.

During these sessions, the research team will record data about:

- How the exercise session went (e.g., game scores, mistakes, reaction time).
- Equipment setup time.

- Any difficulties experienced.

All Participants (Groups 1, 2 and 3):

- In order to assess your recovery, the team will carry out several assessments with you. This means that on some days, we will spend time completing questionnaires (to assess your mental and physical condition).

3. Follow-up (After Discharge)

- After hospital discharge, the research team will contact you.
- The purpose is to arrange a brief follow-up conversation during which some of these questionnaires and tests will be repeated.
- This conversation may take place at the hospital or by telephone, whichever is more convenient for the participant.

Are there any risks or discomforts?

The exercises are considered safe. As with any rehabilitation activity, it is possible that you may feel slight tiredness. Additionally, if you belong to the group using the virtual reality headset, there is a possibility of experiencing discomfort, dizziness, or nausea. If you experience any discomfort, you should inform the team immediately, and the session will be stopped.

Are there any benefits to participating?

Participation in this study may not provide a direct benefit to you. However, the information collected will be very important in helping improve the future recovery of other people who go through the same situation.

What happens to the collected information?

All collected information is confidential and anonymous. Your name or any other identifying information will never be shared or published. The data will be stored securely, with access restricted only to the research team.

What happens to the study results?

The collected data will be analyzed by the research team. The study results will be shared (always anonymously and in groups) with the scientific community, for example, in conferences or publications. Under no circumstances will participants be identifiable.

Recording of Sessions

To better analyze the exercises, we would like to ask for your consent to record the sound (voice) and the screen image of the equipment (tablet or headset) during the sessions. These recordings will be treated anonymously, viewed only by the team, and deleted after analysis.

SIGNATURE OF INFORMED CONSENT

PLEASE COMPLETE THIS AFTER READING THE INFORMED CONSENT AND/OR AFTER LISTENING TO THE EXPLANATION FROM THE RESEARCHER.

Research Project: Cognitive, Physical and Psychological Rehabilitation with Virtual Reality in Intensive Care Survivors.

After having read the informed consent and/or having heard an explanation about this research, by signing this document, I declare that:

- I have read (or had read to me) the informed consent and I understand what to expect regarding my participation in the study “Cognitive, Physical and Psychological Rehabilitation with Virtual Reality in Intensive Care Survivors”.
- I had the opportunity to ask all questions and the answers clarified all my doubts.
- I understand that my participation is voluntary and that I may withdraw at any time, without providing justification and without any prejudice to my healthcare.
- I understand the study procedures, including the assessments (questionnaires and physical tests) and the exercises (with tablet or virtual reality).
- I understand that my personal data are confidential, but that anonymous study results may be used for scientific publication.
- I voluntarily agree to participate in this study.

The research team also requests your permission to record sound (voice) and the screen image (tablet/headset) during the sessions, solely for analysis by the team. Your decision regarding these recordings will not affect your participation in the remainder of the study.

Please indicate your decision:

☐ Yes, I authorise the recording.
☐ No, I do not authorise the recording.

_____	_____
Participant’s Name	**Participant’s Signature**

___/___/___
Date

_____	_____
Legal Representative’s name of the Participant (if applicable)	**Legal Representative’s Signature**

_____
Relationship to the Participant

___/___/___
Date

Researcher / Research Team

The most important aspects of this study were explained to the participant or their representative before requesting their signature. A copy of this document will be provided to them.

_____	_____
Name of the person obtaining consent	**Signature of the person obtaining consent**

___/___/___
Date

Witness (if applicable)

To be completed by an impartial witness if the participant (or their representative) is illiterate. The witness confirms that the document was read and explained in their presence.

_____	_____
Witness Name	**Witness Signature**

___/___/___
Date

Appendix 2

Participation Status and Reason for Loss Codes

Status	Reason for Loss	Description of Reason
Death	DEATH	Death of the participant.
Transferred	TRANS	Permanent transfer to another institution or hospital.
Discharged	DC-HOSP	Definitive hospital discharge before completing the intervention protocol.
Discontinued	D-CLIN	Discontinuation of participation due to a clinically significant worsening of the health condition.
Withdrew consent	W-FC	Active withdrawal declared by the patient/LAR due to fatigue or tiredness.
	W-ACT	Active withdrawal declared because the participant did not wish to continue (reason not specified or not related to fatigue/VR).
	W-RV	Active withdrawal declared due to intolerance or dislike specifically related to the VR intervention.
Loss to Follow-up	L-FU-CF	The patient did not answer or respond to contact attempts after discharge (failure to establish communication).
	L-FU-ERR	Patient contact information was incorrect or outdated.
	L-FU-NO	The patient declined to continue follow-up.

Appendix 3

Master Patient Log

Data Category	Data Variable	Description / Instructions
Identifiers	**Study ID**	Unique participant code transferred from the Screening Log.
	Patient Hospital ID	Clinical ID. PII Security: Access restricted to the research team to maintain confidentiality.
Study Log	**Group Label**	Randomized allocation code (A, B, or C).
	Participation Dates	Start (enrollment/randomization) and End (reaching trial criteria) dates.
	Participation Status	Final study status and, if applicable, the Reason for Loss and Loss Date.
Demographics	**Age, Gender, Education**	Standard demographic markers used for MoCA score normalization.
Acuity Scales	**APACHE II & SOFA**	Clinical severity scores recorded at baseline to assess ICU mortality risk and organ failure.
Clinical History	**ICU Admission Data**	Admission date, primary reason for admission, and specific ICU diagnosis and comorbidities.
ICU Interventions	**Invasive MV (hours)**	Total duration of invasive mechanical ventilation.
	Sedation (Total Days)	Total days of IV/enteral sedation. Notes: Document primary agents (e.g., Dexmedetomidine).
	Analgesia (Total Days)	Total days of IV/enteral analgesics. Notes: Document primary agents (e.g., Morphine).
Clinical Events	**Delirium (YN/Days)**	Incidence (CAM-ICU positive) and total duration of delirium episodes in days.
	Length of Stay (LOS)	Total duration (in days) of both ICU and overall Hospital stay.
Psychosocial	**SSQp_Q4**	Specific data point from the Social Support Questionnaire (short form).

Appendix 4

Level Data Log

Variable	Type	Description / Instructions
Study ID	Alpha-numeric	Unique participant code (e.g., VR_01).
Date	Date	DD/MM/YYYY of the session.
Group Label	Category	Code for the assigned arm (A: VR, B: Tablet).
Session Number	Integer	The sequence of the session (1 through 7).
Game Name	Text	Name of the specific Enhance VR game played.
Level_Number	Integer	The specific level/round within the game.
Level_Duration_s	Numeric	Total time in seconds spent on this specific level.
Level_Score	Integer	Points earned during this level.
Correct_Responses	Integer	Number of successful hits/targets achieved.
Corrections_Before_Hit	Integer	Number of adjustments made before a successful hit.
Total_Errors	Integer	Sum of all mistakes made in the level.
Errors_Commission	Integer	"False positives" (hitting a distractor/wrong target).
Errors_Omission	Integer	Total number of failures due to not responding or technical problems.
Sequence_Errors	Integer	Total times the logic/order of the game was broken.
Longest_Seq_Error	Integer	The maximum number of consecutive errors made.
Avg_Resolution_Time_s	Numeric	Mean time to complete a task/puzzle within the level.
Avg_Reaction_Time_s	Numeric	Mean time between stimulus and first movement.
Spatial_Errors	Integer	Mistakes related to depth or 3D positioning.
Level_Completed_YN	Boolean	Was the level finished successfully? (Yes/No).
Notes	Text	Specific observations.

Appendix 5

Game Data Log

Variable	Type	Description / Instructions
Study ID	Alpha-numeric	Unique participant code.
Date	Date	DD/MM/YYYY.
Group Label	Category	Code for the assigned arm (A: VR, B: Tablet).
Session Number	Integer	The sequence of the session (1–7).
Game_Name	Text	The specific title played (e.g., "Memory Match").
Total_Score	Integer	Cumulative score for the entire game session.
Total_Levels_Comp	Integer	Number of levels successfully finished.
Levels_Zero_Errors	Integer	Count of levels completed with 100% accuracy.
Total_Duration_s	Numeric	Total time spent inside this specific game.
Smoothness	Likert (0-3)	Qualitative rating of fluid vs. jerky movement. 0 – Very smooth: continuous movement 1 – Smooth: small oscillations 2 – Somewhat shaky 3 – Very irregular / segmented
Tremors	Likert (0-3)	Presence and intensity of hand/arm tremors. 0 – Absent 1 – Mild 2 – Moderate 3 – Marked
Bimanual_Coord_YN	Boolean	Did the patient use both hands effectively? (Yes/No).
Symmetry_YN	Boolean	Was the range of motion equal on left and right sides?
Hand_Desync	Likert (0-2)	Did the virtual hands "lag" or lose tracking? 0 – Synchronization 1 – Slight delay between hands 2 – Noticeable delay (one hand works and the other “follows behind”)
Head_Stability	Likert (0-3)	Ability to keep the head steady during gameplay. 0 – Stable 1 – Slight oscillation 2 – Frequent oscillation 3 – Head clearly unstable / not fixed on the target

Head_Hand_Align	Text	Coordination between where the patient looks and reaches. Aligned = the hand moves in the direction the eyes are focused. Misaligned = "drifting" movements, eyes and hands do not coincide.
Mvt_Amplitude	Text	Reach range: Small: movement close to the trunk Medium: movement within the functional zone Large: significant abdication (requires effort)
Compensations_YN	Boolean	Did the patient use trunk/leaning to reach targets?
Rule_Understand	Likert (0-2)	Patient's grasp of game mechanics and objectives. 0 = Understands immediately 1 = Needs reinforcement 2 = Remains confused even after explanation
Assistance_Req	Likert (0-3)	Level of help: 0 – None 1 – Verbal 2 – Physical positioning 3 – Frequent support
Notes	Text	Any additional important information.

Appendix 6

Session Data Log

Variable	Type	Description / Instructions
Study ID	Alpha-numeric	Unique participant code.
Date	Date	DD/MM/YYYY.
Session Number	Integer	Sequence of the session (1–7).
Location	Text	Specific ICU Box or Ward location.
All_Completed_YN	Boolean	Did the patient finish the full 12-minute goal?
Fatigue_Borg_Pre	Scale (0-10)	Fatigue level reported before the session.
Fatigue_Borg_Post	Scale (0-10)	Fatigue level reported after the session.
Engagement	Likert (1-5)	Researcher's rating of patient focus/interest.
HR (Pre/Avg/Post)	Integer	Heart Rate (BPM) at start, middle, and end.
SpO2 (Pre/Avg/Post)	Percentage	Oxygen saturation levels during the session.
BP (Pre/Avg/Post)	mmHg	Arterial Pressure (Systolic/Diastolic).
Temp (Pre/Avg/Post)	Celsius	Body temperature monitoring.
Total_Pauses	Integer	Number of times the game was stopped.
Total_Pause_Time_s	Numeric	Total duration of all interruptions in seconds.
Pause_Reasons	Text	Brief reason(s) for any pauses.
Global_Motor_Perf	Likert (0-3)	By observation, measure the motor Performance at the Beginning vs. End of Session (bimanual coordination, Hand Desynchronization, head stability, movement amplitude, head-hand alignment, smoothness, tremors, amplitude, postural compensations, assistance required). 0 – 0 aspects worsen 1 – 1 aspect worsened 2 – 2/3 aspects worsened 3: ≥4 aspects worsened or session interrupted
Setup_Time_min	Numeric	Minutes from box entry to game start.
Supervisor_Time_min	Numeric	Total minutes the researcher was at the bedside.
Session_Total_min	Numeric	Total time from arrival to departure.
Voided_Code	Code	Reason if the session is excluded.
Adverse_Event	Text	Details of any AE (nausea, agitation, etc.).

CAM_ICU_Result	Boolean	Daily delirium status (Positive/Negative).
VAS_Today	Scale (0-100)	Visual Analogue Scale for general well-being.
Notes	Text	General observations or clinical context.

Appendix 7

Functional Muscle Strength – Self-Report (MRC-Based). This scale is used for remote assessments to estimate the MRC Sum-Score when a physical examination is not possible.

Questions:

1 - Shoulders (Abduction): “Consegue levantar o braço direito/esquerdo até acima do ombro sem ajuda?”

2 - Elbows (Flexion): “Consegue dobrar o braço direito/esquerdo e levar a mão ao ombro direito/esquerdo várias vezes sem dificuldade?”

3 - Wrists (Extension): “Consegue levantar a mão direita/esquerda para trás, como se estivesse a carregar uma bandeja?”

4 - Hips (Flexion): “Consegue levantar o joelho direito/esquerdo para subir um degrau?”

5 - Knees (Extension): “Consegue levantar-se de uma cadeira sem usar os braços, apenas com a perna direita/esquerda?”

6 - Ankles (Dorsiflexion): “Consegue andar em terreno plano sem tropeçar com o pé direito/esquerdo?"