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Evaluation of the effects of a gamified, fully immersive and stroke-specific virtual reality intervention for improving disability and quality of life in patients with stroke in the subacute phase: study protocol of the RESET randomised trial

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ABSTRACT

Stroke is the leading cause of disability and the second cause of death worldwide. The increasing burden of stroke underscores the importance of optimising rehabilitation protocols. Virtual reality (VR) can improve poststroke prognosis. A VR software combining gamification, full immersion and stroke specificity (ie, the Development and validation of a novel viRtual rEality software for improving diSability and quality of lifE in patients with sTroke (RESET) software) might substantially improve disability and quality of life (QoL). However, this technology is still very scarce. The RESET trial aims to assess the effects of an early 10-week gamified, fully immersive and stroke-specific VR intervention (ie, starting at week 3 poststroke) on disability and QoL in people with stroke in the subacute phase. People with ischaemic or haemorrhagic stroke (n=94) aged ≥18 years will be randomised to receive (1) usual care (UC), (2) commercial VR or (3) gamified, fully immersive and stroke-specific VR (*RESET*). The three groups will receive UC (ie, three sessions/week of 90 min of standard rehabilitation). The VR groups will additionally receive three VR sessions of 20 min per week. The outcome measures will be assessed at baseline (week 2 from stroke occurrence), week 13 (approximately 90 days from the event) and week 26 (approximately 6 months from the event). The primary outcome is disability measured with the Barthel Index. Secondary outcomes include QoL, upper-extremity and lower-extremity motor function, gross manual dexterity, handgrip strength and cognitive function. This study will unravel the effects of a gamified, fully immersive and stroke-specific VR software on disability and QoL in patients with stroke in the early subacute phase. Trial registration number: NCT06132399.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Virtual reality (VR) is a promising technology for improving motor and cognitive function in stroke survivors when combined with traditional rehabilitation.
⇒ Some VR software, not tailored specifically for stroke rehabilitation and lacking immersive features, has been previously evaluated as a potential method to improve disability in individuals who have experienced a stroke.

WHAT THIS STUDY ADDS

⇒ The present randomised controlled trial will evaluate the effects of a gamified, fully immersive and stroke-specific VR software tailored to the individual needs of the stroke patient in the subacute phase.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ From a clinical standpoint, if the hypothesis is confirmed, this novel VR intervention will potentially improve current rehabilitation programmes within the healthcare systems for patients who had a stroke.

INTRODUCTION

Stroke—a neurological disease characterised by disrupted brain blood supply leading to oxygen deprivation, brain damage and loss of function—is a global concern ranking as the leading cause of disability and second cause of mortality.[1] Over the past 17 years, the risk of stroke has dramatically increased by 50%, with one out of four individuals expected to experience a stroke in their lifetime.[2] Moreover, over the last 30 years, stroke incidence has risen by 70%, deaths by 43%, prevalence by 102% and disability-adjusted life-Years by 143%,[2] with a 17% increase in age-standardised total stroke incidence.[3] Nearly nine million Europeans live with stroke, costing European countries around €60 billion, and it is expected to rise to €86 billion by 2030.[4]

The growing population of stroke survivors strains healthcare systems due to poststroke complications such as aphasia or motor, cognitive and functional deficits, impacting survivors' quality of life (QoL) and creating a greater demand for rehabilitation services.[5] In 2017, the WHO introduced Rehabilitation 2030—*'a call for action to scale up rehabilitation so that countries can be prepared to address the evolving needs of populations up to 2030'*.[6] Therefore, optimising the rehabilitation process from a holistic perspective seems to be of notorious importance to minimise long-term stroke disability and healthcare resources and simultaneously improve the patients' QoL.[7] However, there is an apparent lack of adherence to standard therapies in patients who had a stroke.[8] Therefore, developing and applying alternative treatment strategies—such as virtual reality (VR)—seems necessary to enhance the motor, functional and cognitive health of patients with stroke.[9]

VR technology offers simulated interactions replicating real-world scenarios or creating controlled and alternative environments,[10] providing a safe, interactive and cost-effective method for addressing a wide range of poststroke complications in neurological rehabilitation.[11 12] Furthermore, VR technology offers high flexibility and control over therapeutic tasks.[13] Within a gamified environment, this technology enables progressive management of the most appropriate dose of rehabilitation, preventing physical and mental fatigue, factors that can deter continued effort and engagement in therapy.[14] VR technology can, therefore, ensure an enjoyable, customised and motivated experience with real-time feedback during therapeutic tasks.[15]

Nevertheless, the VR interventions employed in stroke rehabilitation have been characterised by (1) recreational gaming (eg, Nintendo Wii, Xbox) that is not tailored to address the specific needs of patients who had a stroke and (2) a non-immersive nature, a fact that potentially diminishes the interaction.[16] It has been shown that previous VR interventions have unaddressed methodological issues, such as an inadequate domain-specific outcomes assessment related to the intervention's goals or the absence of outcome assessor blinding.[6] In addition, only a small number of studies have specified the timing of intervention within the stroke phases, which is a key factor because the window of opportunity for enhancing recovery from stroke is larger during the early subacute phase (ie, between 7 days and 3 months after the event).[5] Moreover, it is strongly recommended for the upcoming clinical trials to include endpoint assessments up to 6 months after stroke to fully register the overall patient improvements, disregarding the previous intervention phase and length. However, this has been rarely implemented to date.[6]

A VR software that combines gamification, fully immersiveness and stroke specificity[16] could represent the strongest VR method for improving disability and QoL in people with stroke. However, this hypothesis has not been addressed. Consequently, the full potential of VR technology in improving stroke-related disability and overall QoL remains uncertain.

The primary aim of the Development and validation of a novel viRtual rEality software for improving diSability and quality of lifE in patients with sTroke (RESET) randomised controlled trial is to assess the effects of gamified, fully immersive and stroke-specific VR software on disability and QoL in patients with stroke in the subacute phase. We hypothesise that the RESET VR intervention will improve primary and secondary outcomes compared with the other interventions.

METHODS

Study design

The RESET trial is a three-arm multicentre randomised controlled trial (https://clinicaltrials.gov: NCT06132399). The study protocol follows the standard protocol items: recommendations for interventional trials (SPIRIT) reporting guideline (online supplemental table 1), and the results will be reported according to the consolidated standards of reporting trials (CONSORT) standards (http://www.consort-statement.org/).

Recruitment and eligibility criteria

The participants will be recruited through the Neurology Services of two public hospitals from Southern Spain (ie, Torrecárdenas University Hospital (Almería) and San Cecilio University Hospital (Granada)) at the beginning of the early subacute phase of stroke (ie, 2 weeks after the diagnosis; see figure 1). In case of recruitment issues or time constraints, an additional hospital (ie, Hospital Universitario Virgen de las Nieves, Granada) will be recruited to increase the sample size, if necessary, as a contingency plan. Table 1 presents the eligibility criteria. Participants must meet all the inclusion criteria and have no exclusion criteria to be included.

Randomisation and blinding

After a medical screening, the participants will be randomly allocated (1:1:1 ratio) to either usual care (UC group), commercial VR (CVR group) or gamified, fully immersive and stroke-specific VR (RESET group). To ensure balanced groups and enhance baseline
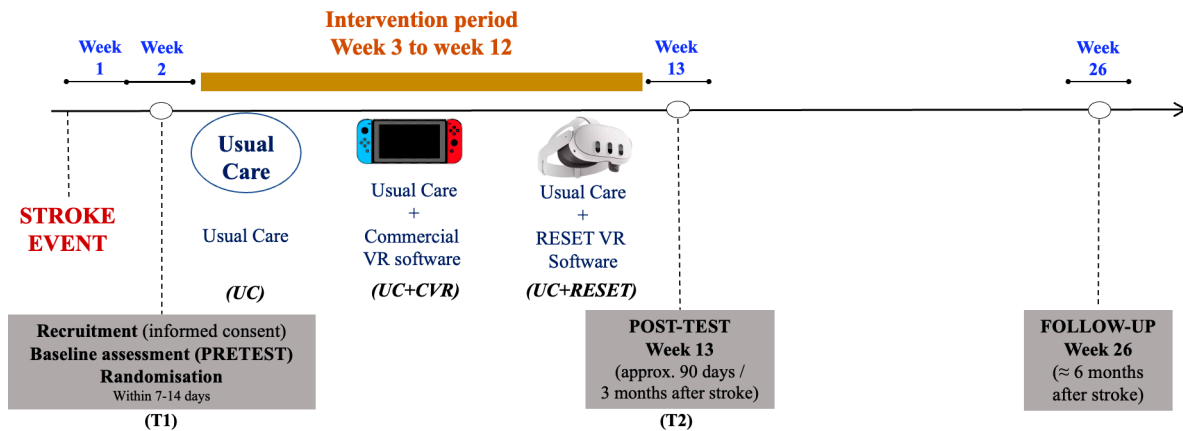
Figure 1 Graphical representation of the RESET randomised clinical trial timeline. CVR, commercial virtual reality; RESET, Development and validation of a novel viRtual rEality software for improving diSability and quality of lifE in patients with sTroke; UC, usual care; VR, virtual reality.

comparability, randomisation in this multicentric trial will be stratified by sex and hospital. A computer-generated randomisation sequence will be created to determine each participant's allocation. Each allocation will be placed in a sequentially numbered, sealed, opaque

Table 1	Eligibility criteria for the RESET project
Inclusion criteria
1. Women and men with either an ischaemic or haemorrhagic stroke
2. Stroke between the last 7 and 14 days
3. Age ≥18 years
4. Functional independence before stroke (modified Ranking scale <3)
5. Paresis of the lower extremity, upper extremity or both, with a score <3 on the 'motor arm' item of the National Institutes of Health Stroke Scale
6. Ability to maintain trunk stability in a seated position
7. Ability to understand basic instructions and to decide whether to sign informed consent
Exclusion criteria
1. Moderate-severe aphasia that precludes understanding the required tasks
2. Cognitive impairment that precludes cooperation with tasks
3. Serious behavioural problems or mental disorders
4. Lower extremity deep vein thrombosis, quadriplegia, neurodegenerative diseases, lower limb fractures or recent myocardial infarction
5. Vital organ (heart, lung, liver, kidney, etc) failure, malignant tumour or other unstable condition
6. A history of cerebrovascular disease (if not fully resolved)
7. Photosensitive epilepsy
RESET, Development and validation of a novel viRtual rEality software for improving diSability and quality of lifE in patients with sTroke.

envelope corresponding to the order of participation randomisation. Randomisation of each participant will occur during their hospital stay and will be conducted by their neurologist after baseline evaluations. The outcome assessors will be blinded to the group allocation. However, due to the nature of the intervention, blinding the participants to the interventions is not possible.

Intervention

The intervention period will last 10 weeks, starting at week 3 following the stroke, to match the recommended temporal endpoint for primary outcome assessment at 3 months.[5] The three intervention groups will undergo UC rehabilitation, following international guidelines[17] and led by physical medicine and rehabilitation physicians. The participants allocated to the VR groups will receive the same total volume of VR exposure, and the intervention will occur within the facilities of the two public hospitals. The participants will be offered transportation to attend the rehabilitation if needed. However, to facilitate recruitment, the participants facing transportation challenges will receive the assigned VR devices (based on group allocation) to conduct the VR sessions at home, provided they have a caregiver to help during the sessions. In these cases, video calls will be supervised by a staff member to ensure the quality of the VR intervention.

The two VR groups will undertake a 2-week familiarisation phase including 2 sessions/week with a duration of 15' to ensure correct adaptation to the VR environment and maximise security. After the familiarisation phase, participants will perform three sessions/week. The duration of VR exposure per session will gradually increase, reaching 20 min according to participants' needs, motivation and capabilities, to prevent cybersickness associated with using VR devices. At both study sites, the VR interventions will be led by a physical medicine and rehabilitation physician and supervised by physical therapists and sports science professionals. To maximise

adherence to the intervention, all the participants will be sent weekly motivational messages via WhatsApp.

Usual care

The UC intervention consists of 3 sessions/week of 90' of physical and occupational therapy conducted by a physiotherapist and an occupational therapist, respectively. The exercises comprise (1) active-assessed mobilisation and strengthening of the paretic musculature, (2) relaxation of spastic musculature if present, (3) proprioceptive stimuli in the affected hemibody, (4) trunk control in seated position and standing position, (5) re-education of balance in both a standing position and during gait, (6) task-oriented training, (7) facilitating basic activities of daily living, (8) compensatory techniques for the deficit and (9) speech therapy in cases of mild aphasia. The UC rehabilitation begins within 48–72 hours following the stroke and continues up to week 26 (6 months; the beginning of the chronic stage of recovery) according to the participant's recovery. To ensure that all participants receive UC during the entire trial intervention period, the minimal duration of rehabilitation will be 12 weeks from stroke.

Commercial non-immersive VR group (UC+CVR)

This group will use the Nintendo Switch (Nintendo, Kyoto, Japan) gaming system with the Sports package games. This gaming system continues the former Nintendo Wii, which is widely used for VR rehabilitation worldwide[18] but is no longer available. The participants will be requested to play various games, including soccer, volleyball, bowling, tennis, badminton and chambara (swordplay) to address different rehabilitation dimensions. As the intervention progresses, they will be invited to select different levels of the games based on their capabilities and interests to enhance motor recovery and function.

Gamified, fully immersive and stroke-specific VR group (UC+RESET)

The RESET VR software is being developed by a project team composed of computer programmers and game designers (NeuroRehab, Dynamics VR Rehab, Sevilla, Spain), professionals in physical activity and sports sciences (University of Almería and University of Granada; Spain), and medical doctors including rehabilitation physician and neurologists (University Hospital San Cecilio, University Hospital Torrecárdenas; Spain). This software will be integrated into the META QUEST 3 glasses (Meta Platforms, San Francisco, California, USA; figure 2). The RESET VR software includes specific modules covering domains such as gross motor control, fine motor control, balance, rhythmic movements, movement speed, memory attention and cognitive speed. These domains will be addressed through activities designed for diverse virtual environments, each incorporating a challenge component. The programme will integrate gamified procedures, including simulations of

Figure 2 META QUEST 3 glasses that will be purchased and used for testing and implementing the RESET virtual reality software.

everyday activities and games set in fantasy environments. Task progression will be reached by incremental achievements on an individual basis, with the patient receiving scores and targeted improvement feedback to optimise motivation. The embedded personalised feedback system will facilitate this customised advancement within the software. The software will incorporate visual and auditory instructions to enhance the patient's autonomy throughout the therapeutic process. Furthermore, considering that the intervention is focused on the early subacute phase of stroke in which most patients suffer hand/arm impairments, the software will implement a hand tracking system to facilitate the patient experience within the VR environment.

Data collection

Assessment protocol

The entire set of assessments will be performed on three separate occasions corresponding to major clinical temporal endpoints for stroke recovery[19] (figure 1). The outcomes that will be assessed are summarised in table 2. The full set of outcome assessments will be performed at baseline (T1; week 2 after the stroke event), week 13 (ie, after the intervention period; ~90 days after the stroke event: primary endpoint) and week 26 (ie, 6 months after the stroke event). This schedule of temporal endpoints has been internationally recommended in high-profile publications to enhance the quality of upcoming clinical trials in this field.[5] The same instruments and tests will be used for all the participants, regardless of the group allocation. All the tests and questionnaires selected have been previously validated and are commonly used in research protocols. A qualified medical team with support from physiotherapists and sports sciences professionals will lead all the assessments using the secure electronic platform Research Electronic Data Capture. Continuous communication will be maintained via WhatsApp to enhance participant retention during the assessment period. Assessments will be conducted at the same location as interventions, with flexible scheduling options available. On recruitment, participants will receive a comprehensive infographic detailing the assessment procedures.

Table 2 Primary and secondary endpoints of RESET project

Endpoints	Description
Primary endpoint	
Physical disability	Barthel Index Questionnaire[20]
Secondary endpoints	
Quality of life	Spanish version of the Newcastle Stroke-Specific Quality of Life Measure[21]
Upper extremity function	Fugl-Meyer assessment of Upper Extremity[22]
Gross manual dexterity	Box and Block Test[23]
Handgrip strength	Digital dynamometry[24]
Lower extremity function	Berg Balance Scaled[25] and the Time Up and Go Test[26]
Cognitive function	MOCA[27] and Trail-Making Test[28]

MOCA, Montreal Cognitive Assessment; RESET, Development and validation of a novel viRtual rEality software for improving diSability and quality of lifE in patients with sTroke.

Primary outcome
Disability
The primary outcome of the RESET study is disability at week 13, assessed with the Barthel index.[20] The Barthel index is an ordinal scale used to measure performance in activities of daily living. It consists of 10 everyday activities, comprising 8 related to personal care and 2 related to mobility. These are assessed for independence/dependence and scored via an arbitrary weighting system—the index yields a total score out of 100—the higher the score, the lower the degree of disability.

Secondary outcomes
Quality of life
Stroke-specific QoL will be assessed with the Spanish version of the Newcastle Stroke-Specific Quality of Life Measure,[21] a patient-derived, interviewer-administered, specific health-related QoL measure of 56 items grouped into 11 domains: feelings; activities of daily living (ADL)/self-care; cognition; mobility; emotion; sleep; interpersonal relationships; communication; pain/sensation; vision; and fatigue. Each individual item is rated 0–3 and has not an isolated specific meaning. Domain results are the sum of item scores, where higher values indicate lower QoL.

Upper extremity motor function
The upper extremity motor function will be assessed with the Fugl-Meyer assessment of Upper Extremity.[22] The test consists of 33 items that evaluate the shoulder, elbow, forearm, wrist and hand movement, coordination and reflex action. Each item is scored on a 3-point scale (0=cannot perform, 1=performs partially and 2=performs fully) and the total score ranges from a minimum of 0 (hemiplegia) to a maximum of 66 points, with higher scores indicating better motion function.

Gross manual dexterity
Gross manual dexterity will be assessed with the Box and Block Test.[23] The participant will be seated at a table, facing a rectangular box divided into two square compartments of equal dimension by a partition. 150 blocks (2.5 cm) will be placed in one compartment. The patient will be instructed to move as many blocks as possible, one at a time, from one compartment to the other for 60 s. The score will correspond to the number of blocks moved from one compartment to the other during the trial time. The patient's hand must cross over the partition for a point to be given. Multiple blocks carried over simultaneously will count as a single point. Higher scores indicate better gross manual dexterity.

Handgrip strength
Digital dynamometry (JAMAR+Digital Hand Dynamometer) will perform the handgrip strength test. The test protocol will be performed as described elsewhere in patients who had a stroke.[24] Participants will execute three trials with each hand, and the best score for each hand will be considered the maximal strength and will be used for the analyses. The maximal strength values obtained from the non-paretic side will be a reference for comparisons with the paretic side.

Lower extremity function
The lower extremity function will be assessed with the Berg Balance Scale[25] and the Time Up and Go test.[26] The Berg Balance Scale is a quantitative assessment of balance in older adults. The scale consists of 14 items requiring individuals to maintain positions or complete movement tasks (common to everyday life) of varying difficulty levels. Each item receives a score of 0–4 based on the ability to meet the test's specific time and distance requirements, where 4 represents the ability to complete it independently. The Time Up and Go assesses the ability to perform sequential motor tasks relative to walking and turning. This test requires participants to stand up from a chair, walk 3 m, turn around, walk back to the chair and sit in the minimum possible time. A trained evaluator will register the time taken to complete the test with a chronometer.

Cognitive function
The Montreal Cognitive Assessment (MOCA) will assess the cognitive function.[27] The MOCA consists of 30 simple questions/tasks, and they are grouped into eight cognitive domains: visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall and orientation. The total score ranges from 0 to 30, with higher scores indicating better cognitive function.

The Trail-Making test[28] will assess the executive function, visual scanning and graphomotor speed. Successful performance of this test requires letter and number recognition, mental flexibility, visual scanning and

motor function. Part A requires the patient to connect randomly 25 numbered circles in numeric order as quickly as possible. In part B, the participant must draw lines to connect the 25 circled numbers and letters in an alternating numeric and alphabetic sequence (ie, 1, A, 2, B, 3 and C) as rapidly as possible. The time to complete the task (in seconds), and the number of errors, will be recorded. Longer time indicates greater impairment. A maximum time of 100s is typically allowed in part A and 300 for part B.

Patient and public involvement

Patients with stroke are continuously engaged in the key stages of this study: first, through the planning stage, where patients actively participate; then, during the RESET software development phase where patients participate in team meetings and provide their feedback; and finally, their involvement continues in the implementation and dissemination phases. During the development phase, multiple meetings are organised, each involving 3–5 patients, computer programmers, game designers, neurologists, physical medicine and rehabilitation specialists, and sports sciences professionals. These meetings are intended to test the software's improvements and acquire feedback from people with stroke. We are considering their experience and feedback about task difficulty, immersion, embodiment, enjoyment and the software's utility for recovery from stroke. Following these insights, the project team evaluates possible software refinements, and the game designers and programmers implement appropriate software modifications for testing in the next meeting. In addition, the main findings of the RESET trial will be communicated to people with stroke through patients' associations and healthcare centres. The results of this project will be presented at international congresses, seminars, social media interviews, conferences and scientific journals.

Patient's experience and autonomy using VR interventions

To assess the satisfaction levels of the patients and caregivers using the VR devices (including both the Nintendo Switch and the RESET software), we will use the Net Promoter Score,[29] a straightforward tool which ranges from 0 to 10 points indicating the spectrum of satisfaction and dissatisfaction. Participants will respond to the following question: How likely are you to recommend the RESET VR software/Nintendo Switch to other persons recovering from a stroke?

Additionally, the frequency of patients seeking assistance to perform tasks will be recorded to evaluate the autonomy level using the VR RESET software and the Nintendo Switch during rehabilitation sessions.

Patient safety
Adverse events
Throughout the study, any potential adverse consequence directly associated with the intervention will be reported, and the adverse events will be systematically registered. Death, life-threatening events (eg, stroke, myocardial infarction and fracture), hospital readmissions or new disability leading to prolongation of existing hospitalisation will be considered serious adverse events. Intervention-related dizziness, light-headedness, back or shoulder pain, or muscle aches during the study period will be considered minor adverse events.

Criteria for interrupting study participation
Any participant may leave the study without explanation and consequences for their medical care or treatments received. The research team may discontinue any patient's participation (a withdrawn participant) if the patient poses a risk to their safety or if a violation of the study protocol is produced. This can occur under the following circumstances: (1) Severe skeletal muscle injury that alters the participant's normal lifestyle (as a consequence, or not, of participating in the study); (2) Severe diseases that preclude undertaking rehabilitation (eg, COVID-19-related pneumonia); (3) A change of residence, making all postoperative assessments impossible and (4) Death.

Data management and statistical analysis
The sample size was calculated with G*Power V.3.1 (Düsseldorf University) for a within-factors repeated measures analysis of variance in the primary outcome (Barthel index total score). Based on an estimated effect size (Cohen's f) of 0.35 and considering a power of 80% and an α error of 5%, a total of 81 patients who had a stroke would be needed (approximately 27 per group). Considering a potential 15% drop-out rate, we will recruit around 94 patients. According to previous records, the neurology units at the two study hospitals receive >400 patients who had a stroke annually, and we anticipate recruiting approximately 10–12 patients per month (5–6 at each site) for 9 months.

The primary outcome will be analysed with an intention-to-treat approach. The between-group differences (RESET vs UC; RESET vs CVR; and CVR vs UC) in the primary and secondary outcomes at week 13 and week 26 will be determined with a repeated measures general linear model adjusted for baseline values if necessary. For each comparison, the between-group difference (95% CI) and the level of statistical significance will be presented, together with the standardised effect size (Cohen's d). A two-sided $p<0.05$ will be considered statistically significant. Sensitivity analyses will also be performed using a per-protocol procedure (participants will be included if they attended ≥75% of the sessions) to check the robustness and consistency of the results. We will conduct exploratory analyses to address the potential interaction by sex, although we do not expect to observe sex differences in the effects of the intervention.[17] The analyses will be performed with Stata V.16 and R. Based on the study's structure, sample size, our research team's extensive experience in data management, and this clinical trial does not involve drugs, we determined that a

data monitoring committee will not be required. The statistical analyses will be conducted by researchers blinded to the group allocation.

POTENTIAL IMPACT OF THE RESET STUDY

The persistent and substantial increase in the incidence of stroke presents many challenges for governments and healthcare systems worldwide that require immediate attention.[5] Indeed, the demands on the healthcare system resulting from stroke impact are escalating, underscoring the growing importance of advancing rehabilitation therapies.[4] To the best of our knowledge, the RESET study will assess, for the first time, the effects of a gamified, fully immersive and stroke-specific VR intervention on disability and QoL during the early subacute phase of stroke. Previous studies have demonstrated some advantages of using VR technology in addition to UC within some dimensions of stroke rehabilitation.[9] However, most previous clinical trials suffer from methodological constraints,[30] and a specialised tool tailored to rehabilitate stroke-related consequences through a fully immersive gaming experience is currently lacking.

This study will assess the impact of implementing the RESET software for improving disability, QoL and different functional and cognitive outcomes among people with stroke and compare the results with UC and other VR devices that have been shown to improve functional outcomes. With the implementation of a comprehensive, individualised and specific software for stroke rehabilitation, we anticipate a positive impact on patient adherence to rehabilitation protocols. Furthermore, the incorporation of this VR device has the potential to facilitate a significant degree of autonomous rehabilitation, which could partly reduce therapist supervision. This feature becomes particularly valuable in healthcare systems with limited resources and increasing volume of patient.[12] Moreover, we can evaluate the intervention's efficacy in the early stages following a stroke, a critical period of spontaneous biological recovery.[30] In preparation for the clinical trial, we are also conducting preliminary tests with patients to enhance the software, which is informed by valuable patient feedback. The RESET study aims to overcome numerous limitations from previous studies and provide novel and valuable insights for developing new treatment strategies based on VR for people with stroke.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The study has been approved by the Human Research Ethics by the Ethics Committee for Clinical Research in the province of Almería (118/2023). Significant changes will be reported to the ethics committee. Eligible participants and their caregivers will receive written and oral information about the study. All participants will be required to sign the informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. This is a study protocol; therefore, no original data are available.

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