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Title:

Feasibility and preliminary results on the effect of an immersive virtual reality-based vestibular rehabilitation program for dizziness, balance and fatigue improvement in people with multiple sclerosis: protocol for a pilot randomised controlled trial.

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TITLE

Feasibility and preliminary results on the effect of an immersive virtual reality-based vestibular rehabilitation program for dizziness, balance and fatigue improvement in people with multiple sclerosis: protocol for a pilot randomised controlled trial.

ABSTRACT

Introduction

Vestibular impairments could explain dizziness, balance disorder and fatigue in multiple sclerosis (MS) subjects. Vestibular system damage may have a central and/or peripheral origin in this disease. Thus, this population could benefit from a vestibular rehabilitation program to improve these symptoms. As a successful tool in neurologic rehabilitation, virtual reality (VR) could also be implemented within a vestibular rehabilitation intervention.

Methods and analysis

This protocol describes a pilot randomized controlled trial with a single-blinded and two-arms design. The assessor will be blinded to participant allocation. At least 30 MS participants that meet all eligible criteria will be recruited and randomly assigned to one of the two groups of study. The experimental group will receive an immersive virtual reality (VRi) vestibular rehabilitation intervention based on the Cawthorne-Cooksey vestibular rehabilitation protocol; the control group will be provided by this conventional protocol. Each group will receive 3 sessions per week, each of 50 minutes, performing a total of 20 sessions (10 session for initial phase and another 10 for advance phase). The primary outcomes are feasibility and safety of the vestibular VRi intervention in MS patients. Secondary outcomes measures are the changes in dizziness symptoms, balance performance, fatigue and quality of life. Evaluations will be carried out at baseline, immediately after intervention and after a follow-up period of 3 and 6 months.

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). Informed consent will be provided to those participants who wish to be part of the research. Results of the research will be disseminated through peer-reviewed scientific journals.

Trial registration number ClinicalTrials.gov NCT04497025.

Keywords: multiple sclerosis; vestibular diseases; dizziness; postural balance; fatigue; physical therapy modalities; virtual reality.

Strengths and limitations of the study

- This study addresses a relevant gap regarding the improvement of dizziness, balance and fatigue in MS patients through VRi.
- As the VRi intervention is developed and based on the Cawthorne- Cooksey conventional vestibular rehabilitation protocol, it allows a homogeneous comparison between study groups.
- Thanks to the intrinsic characteristics of VRi, this protocol could overcome the limitations of the original vestibular exercises protocol.
- Blinding of participants and therapists is not possible due to the type of intervention.

INTRODUCTION

Multiple sclerosis (MS) is defined as a chronic autoimmune disease characterized by inflammation and demyelination of the central nervous system and axonal loss [1,2]. It affects more than 2.5 million people worldwide, being one of the main non-traumatic cause of disability in young adults [3–5]. Balance disorders, dizziness and fatigue are among the most common and troublesome symptoms and in MS repercussing on quality of life [2,6–10].

Balance problems, lack of coordination in cephalic movement with regard to the body, ocular disturbances and dizziness are symptoms related to vestibular system disorders [11–13]. Postural problems could be associated to the altered reflex answered of vestibulo-ocular reflex (VOR) and vestibulo-spinal reflex (VSR) [14–16]. Central demyelination and/or peripheral disturbances can be possible aetiologies of vestibular impairments in MS [17,18]. MS patients could benefit from the goals of vestibular rehabilitation: decrease dizziness, improve ocular fixation, improve stability and its effects on daily living activities [19–22].

Vestibular rehabilitation are exercises that provide accurate spatial information of the head with regard to body position while stimulating a VOR, VSR and somatosensory information [7,20,23–25]. Vestibular rehabilitation is based on mechanisms of substitution, adaptation and habituation [20,26], which appear to be helpful in both peripheral and central vestibular impairments [18,27,28].

The effectiveness of conventional vestibular rehabilitation in improving dizziness, balance and fatigue in patients with MS has recently been demonstrated through the publication of a meta-analysis [29]. Conversely, in the current scientific literature there is an exponential growth in the number of studies that evaluate the usefulness of virtual reality (VR) applied to vestibular rehabilitation in other diseases [30–38]. The usefulness of non-immersive VR for balance and gait training has already been specifically proven for MS patients [39]. To the best of our knowledge, no previous research of immersive virtual reality (VRi) and vestibular rehabilitation in MS has been performed. VRi allows the subject a complete immersion within the 360º virtual environment, enhancing the feeling of presence [40–42]. Several authors as Meldrum et al. [43] declare the need to develop a standardized virtual reality intervention protocol of vestibular rehabilitation

and to strength the evidence of vestibular approach in MS population [44–46].

Because of that, we develop a VRi vestibular protocol in MS. Thus, the primary purpose of this study is to determine the feasibility and safety of a VRi-based vestibular rehabilitation program in MS population. Secondary, we aim to evaluate preliminarily the effects of vestibular VRi exercises protocol in comparison to conventional vestibular training for the improvement of dizziness, balance and fatigue in people with MS.

We hypothesize that VRi intervention will be feasible, safe and well tolerated by the participants. Also, we hypothesize that VRi experimental intervention will be at least as effective as the traditional Cawthorne-Cooksey vestibular exercise protocol.

METHODS AND ANALYSIS

Study design

This protocol describes a two-arm parallel group design and single-blinded pilot randomized clinical trial (RCT). To avoid vias during randomization, asessors will be blinded to the group allocation. The future pilot RCT is a prospective study, with an initial evaluation of the sample before intervention, followed by an intervention period of 7 weeks. A further three evaluations will then be carried out: immediately after intervention and after a period of 3 and 6 months of follow-up. The study design is represented in Figure 1.

This protocol meets the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [47]. This RCT will also be developed following instructions from the Consolidated Standards of Reporting Trials (CONSORT) [48]. It has been registered at ClinicalTrials.gov with the identifier NCT04497025.

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Sevilla (Spain). The Virgen Macarena Hospital will be the main healthcare institution involved in this research. The inclusion of other healthcare centres in the area is expected.

Participants and recruitment

Recruitment of participants is expected to start in September 2021 and is estimated to be completed in September 2022. It will be carried out in the participants' healthcare institutions. The research team will begin by contacting the physical therapists and medical directors of each centre. All subjects that potentially meet the eligibility criteria will then be contacted and invited by phone to participate in the study. After given oral and written information to the subjects, they will be given the freedom to decide if they wish to participate. Finally, those people with MS who wish to participate in this study and meet the eligibility criteria will be given written informed consent (please see supplemental material for informed consent form).

Inclusion Criteria:

• Both male and female subjects from 18-65 years old
• Clinically diagnosed with any type of MS in accordance with the revised McDonald criteria. This will be assessed by clinic history and a medical team.
• With walking ability according to the Expanded Disability Status Scale score (EDSS≤6). This will be assessed by clinic history and a medical team.
• With the objective presence of dizziness symptoms (Dizziness Handicap Inventory ≥16). This will be assessed after informed consent acceptance by an expert vestibular physical therapist.

Exclusion Criteria:

• Partial or complete blindness
• Cognitive impairment (Mini Mental State Examination ≤24)
• Another neurologic disorder contributing to balance impairment
• Disease flare within the last 3 months
• Changes in MS pharmacotherapy within the last 3 months
• History of vestibular rehabilitation within the last 6 months
• Acute cardiovascular or respiratory illness.
• Any other contraindication to physical activity
Exclusion criteria will be assessed by clinic history and a medical team.

Randomisation, concealment allocation and blinding

Participants will be randomly allocated to one of the two intervention groups by an independent researcher. We will consider a 1:1 distribution ratio and a computer-generated random sequence will be used. We will conduct a concealed group order allocation using sealed envelopes, and the assessor will remain blinded to the participant´s group.

Patient and public involvement

No patients or public are involved in designing the trial, but a number of public organisations are contacted for patient recruitment (e.g: Hospital Virgen Macarena, Ilustre Colegio Profesional de Fisioterapeutas de Andalucía). Once the results are published, participants will be informed about them by e-mail in an understandable writing; furthermore, the researchers will perform meetings in each public organisation engaged for recruitment

Interventions

Conventional Vestibular Rehabilitation Protocol (CG)

The control group will perform the conventional vestibular rehabilitation Cawthorne-Cooksey protocol exercises, which have been used to develop the experimental intervention as well [23]. These exercises aimed to restore balance affected by a vestibular dysfunction or to train the vestibular system. This improves vestibular compensation through a mechanism of neuroplasticity known as adaptation, habituation and substitution. The primary goal of these mechanisms is to adapt the VOR and VSR, to

habituate and substitute head movements that provoke vestibular and balance symptoms, and to train dynamic balance.

As shown in Table 1, exercises are divided into three blocks, which will be performed slowly at first and then faster. Participants allocated in the CG will receive this conventional protocol 3 times per week, for 7 weeks. Each session will last 50 minutes, and the rest time will be at least 5 minutes. A total of the 10 initial sessions and 10 advanced sessions will be carried out. Based on previous studies, during the initial phase, exercises of the first and second block will be carried out by 10 slow repetitions and 10 fast repetitions [49,50]. The third block exercises will be repeated 5 times slowly and then 5 times more quickly. The complete time of intervention for each block is 15 minutes (Table 1). Once participants have exceeded the first ten sessions, they will begin with more complex exercises. To developed these advanced vestibular exercises for both groups, Cawthorne-Cooksey [23], Han et al. [19] and Whitney et al. [51] principles and keys for this type of rehabilitation were assumed. The advanced phase of intervention for participants allocated in the control group is described in Table 2. This intervention matches with the EG with the only difference that exercises are not performed at an immersive virtual environment. Some parameters of exercises modified along the vestibular advanced sessions will be the base of support width, standing on unstable surface, alternatives single leg support, tandem position, increased velocity of head movements, higher head range motion and coordinated movements with arms and trunk. These parameters provide proprioceptive disturbances, encouraging vestibular training through substitution neural mechanisms.

The vestibular program will be conducted by an experienced vestibular rehabilitation physical therapist, who will give verbal indications and stay near the participants to provide them with confidence and decrease the risk of falling during the session.

Immersive Virtual Reality Intervention (EG)

Participants assigned to EG will receive a VRi vestibular rehabilitation through the head mounted display (HMD) Oculus Quest. VRi allows complete immersion in a 360º virtual environment and enables interaction. A virtual immersive rehabilitation can only be obtained with the use of VR glasses or a head mounted display (HMD). In this protocol, the new generation Oculus Quest equipment has been selected, which has some added advantages compared to other similar HMDs. These advantages include absence of movement sensors or laptop installations, wireless, portable and a reduced risk of suffering from cybersickness syndrome, thanks to the high resolution and accurate movement capture [52,53].

In order to achieve homogeneous interventions over the two groups, VRi intervention have been designed based on the gold standard Cawthorne-Cooksey vestibular protocol. Subjects in this group will receive the same number of sessions and duration than the CG. Just like CG, first 10 sessions of the VRi treatment will be carried out in sit down position (eyes and head movement/ head and body movement) and last one standing up exercises. Numbers of repetitions and adaptation of VRi equated to conventional protocol to immersive virtual environments during initial phase are described in Table 1. As initial

phase, the advance phase exercises will be the same in both groups with the main different of the interaction with immersive virtual environment. Advance phase of vestibular rehabilitation and the VRi adapted exercises are shown in Table 2. Same exercises parameters described in CG will be applied in EG. Also, to prevent falls over the interaction with virtual environments participants will be monitored and supervised by an expert physical therapist.

First Steps, Beat Saber demo and Sport Scrambles demo games will be displayed in the Oculus Quest Virtual Glasses to apply the vestibular protocol. These games respond to a first person exergame intervention in which subject actions are simultaneously recreated inside the virtual environment. Furthermore, all selected games are commercially available and are free access in the Oculus App to anyone who owns an HMD device. *First Steps* is the onset game of Oculus in which you learn to use the VRi device in a playable way. This game is constituted by the *Main room* where the subject can interact with virtual objects as virtual blocks, pin-pong racket and ball, hanging ball, etc. Also, it contains two more virtual environments within the videogame. The first one is a shooter game called *Shots in the Space*, which aim is to reach the highest score while you are shooting random targets at a Space Station. This shooter offers three options: a single gun, a double gun, or a machine gun. The second one is *Dance with Robot* in which you dance and interact with a robot following some indications. *Beat saber* is a rhythm music game in which you slash some blocks in a specific direction with a red (left hand) and blue (right hand) saber, meanwhile you try to avoid some obstacles. Sport Scrambles consist in three sports games: baseball, tennis and bowling in which you must defeat your opponent even when balls, rackets or your baseball bat are randomly changing into a giraffe, a cheese, so on. Virtual scenarios are shown in Figure 2.

Outcomes and measurements

Primary outcomes will include the feasibility and safety of the experimental VRi vestibular protocol. Feasibility of study will be assessed by participation rates, participant retention, adherence to treatment and usability of the VRi device. Safety will be examined by the appearance of cybersickness along the virtual reality treatment and a registry of falls and other adverse events.

Secondary outcomes are driven to assess the changes in dizziness, balance, fatigue and quality of life after a VRi vestibular protocol compared to conventional vestibular rehabilitation.

Usability of the Virtual Reality System

In combination with participation, retention and adherence to treatment rates, feasibility will be evaluated by The System Usability Scale (SUS). SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means strongly disagree and 5 means strongly agree. The overall score can range from 0 to 100, which is obtained by multiplying the sum of every item by 2.5. A higher score means a higher usability [54,55]. To maintain the blindness of

assessor, this measurement will be performed after by the physiotherapist who conducted the intervention.

Cybersickness Syndrome

To assess safety of the intervention along with fall and adverse events registry, the appearance of cybersickness will be evaluated by the Simulator Sickness Questionnaire (SSQ). SSQ will be implemented to measure the appearance of sickness due to the virtual environment. The SSQ consists of a 16-item questionnaire divided into 3 categories: nausea, oculomotor and disorientation [56,57]. Scores ranging between 10 and 15 mean significant symptoms, and above 20 indicates a simulator problem [58]. This scale will be provided by the physical therapist on each session.

Dizziness

Dizziness symptoms will be assessed using the Dizziness Handicap Inventory. This is a self-assessment questionnaire of 25-items, divided in the following subscales: physical, emotional and functional. Physical and emotional subscales range from 0 to 36 points, and the functional subscale ranges from 0 to 28 points. The total score is 100, which relates to the highest level of disability and handicap [59–61]. This instrument is reliable and valid for the studied population [62,63].

Balance

Static balance will be evaluated by the Biodex Balance System. The mentioned balance system allows registration of the location of the centre of pressure (CoP) [64–66]. Biodex has been proven to be a valid instrument to evaluate stability and postural control in MS subjects [67,68]. Moreover, Biodex can compute the following variables in relation to the CoP:

- Length (mm) is the CoP trajectory through all the platform surface.
- Anteroposterior (SAP) and mediolateral sway (SMS) measure CoP deviation along each axes (mm).
- Velocity (mm/s) of oscillation of CoP through anteroposterior axis (VAP) and mediolaterally (VML).
- Each variable will be assessed in open/close eyes conditions and firm/foam surface, respectively.

The Berg Balance Scale (BBS) is the selected instrument to measure dynamic balance. BBS is constituted by 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance [69,70]. This assesses the skill to sit, stand, lean, turn and stand on a monopodal support. For the study population, BBS proved to be reliable and valid [62,63].

Fatigue

The Modified Fatigue Impact Scale (MFIS) is a self-reported questionnaire that evaluates the perceived impact of fatigue in MS patients. This scale is composed of 21-items which

assess fatigue impact in three different domains. The global scale is divided into 9, 10 and 2 items that belong to the physical, cognitive and psychosocial domain, respectively. The total score is 84, and higher scores mean a higher impact of fatigue [71,72]. This scale is reliable and valid to measure impact fatigue in MS subjects [73,74].

Quality of Life

To assess the changes perceived by participants in their quality of life, the reliable and valid Multiple Sclerosis Quality of Life Scale 54 (MSQoL-54) will be used [75]. This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score range is from 0 to 100 scales. Higher values indicate better quality of life [76].

Data will be collected by a blinded physical therapist who is an expert in neurological and vestibular rehabilitation. The blind evaluation will be performed at several points in the study: before the intervention, at the end of the intervention and 3 and 6 months post-intervention (Table 3).

Sample size calculation

A major reason for conducting a pilot study is to determine initial data in order to perform a sample size calculation for a larger trial [77]. For this reason, a formal sample size is not calculated. However, following the recommendations of good practice for the design and analysis of feasibility and pilot studies in preparation for RCT [77, 78], we aim to recruit at least 30 subjects (15/group).

Statistical analysis

Normal distribution of the variables will be assessed by the Shapiro-Wilk Test, and the Levene Test will be carried out for the variance homogeneity. The description of quantitative variables will draw on central tendency measures and dispersion as mean and standard deviation, when they follow a normal distribution. When variables do not follow this distribution, median, minimum and maximum intervals and percentiles, which are of interest for research purposes, will be reported. Additionally, the results of qualitative variables will be shown as absolute and relative frequencies.

For normal distribution, the Student t-test will be implemented to compare means of independent-samples. On the other hand, similar non-parametric tests will be applied in case of non-normal distribution. The Cohen criteria will be followed to assess the effect size of the studied variables. 95% confidence intervals will be considered. The intention-to-treat principles will be considered for all analyses. Graphical and numerical analysis of the data will be conducted using SPSS 25.0 (IBM Corp, Armonk, NY, USA) and GraphPad PRISM (GraphPad Inc, San Diego, CA, USA).

Data management and monitoring

The research will not have an established data monitoring committee because main decisions will be consensual between investigators. All data will be codified and recorded

in an encrypted database by a number (in step of the name for example) known only by researcher team. Data will not be disclosed to third parties without participant consent.

Falls or any other adverse events derived along the intervention will be recorded by the therapists in a registry. These events will be communicated to principal investigator of study.

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). All participants will undergo and accept informed consent before data compilation. The investigators will disseminate the study results via publication in peer-reviewed scientific journals.

DISCUSSION

The current protocol for this pilot RCT aims to assess the feasibility and safety of a vestibular rehabilitation in patients with MS through an immersive virtual reality intervention compared to the conventional approach. Likewise, we will evaluate the changes occurred in dizziness, postural control and fatigue for both study groups after the vestibular intervention.

Although, VR is a booming tool in scientific literature for neurorehabilitation and vestibular rehabilitation, the immersive systems have been poorly studied before and no previous researches are found in MS population [43,79,80]. Nevertheless, now with affordable prices, current VRi devices own a high-resolution graphics, higher frames per second, less delay and latency, and an accurate software and hardware [81,82]. All this enhance the sense of presence and immersion of the subject and reduce the possible appearance of cybersickness as Weech et al. [83] confirm. Thanks to VRi tracking (gyroscopes, accelerometers and magnetometer) and software systems that record head and corporal movements in six degrees of freedom, it is possible to perform exercises in different postural circumstances, just as our experimental protocol (sit down, standing, single leg support, tandem and standing on foam surface). All this ensure virtual environment verticality by automatic adaptations. [53,84]. Furthermore, the command centre of movements and multisensorial stimulation are primarily found at cephalic level in HMD, becoming VRi a suitable device for vestibular rehabilitation [57,85–87].

Concerning to vestibular rehabilitation, authors as Zeigelboim et al. [88] and Pavan et al. [89] declared that that the specific vestibular exercises protocol developed by Cawthorne-Cooksey improved dizziness and vertigo in MS patients [90,91] . Additionally, Afrasiabir et al. [49] and Karami et al. [50] support that Cawthorne-Cooksey vestibular training improved fatigue and enhance balance of MS patients, respectively. This gold standard protocol was the one selected as our control group intervention and taken as the reference to develop the VRi vestibular intervention for the experimental group, owing to its demonstrated effectiveness. Furthermore, this one presents some limitations solved through VRi and its multimodal variant by providing extrinsic feedback during exercise execution, cognitive and task-oriented training, multisensorial stimulation and avoiding

humdrum exercise repetitions thank to motivational and enjoyable environment. The recent systematic review of Soltani et al. [92] supports the HMD as a feasible and safety intervention to improve balance in older adults, because of this we expected that VRi vestibular intervention will be safe and feasible in MS population [45,93–95].

Viziano et al. [34] and Micarelli et al. [33] studied the effect on unilateral vestibular hypofunction after a smartphone HMD vestibular intervention combined with conventional vestibular therapy compared to conventional approach. Both authors reported significant differences in dizziness and balance between groups in favours of smartphone HMD group ($p < 0.001$). These beneficial effects are forecast for VRi headsets which hold better usability results than smartphones or monitors [96,97]. Moreover, VRi headset as Oculus are associated to a minor presence of cybersickness than smartphones HMD [98].

Regarding the application of VRi strategies in MS, the study of Ozkul et al. [99] showed better results for balance and fatigue in participant allocated in VRi balance intervention than conventional balance training or Jacobson's progressive relaxation exercise, respectively. However, interventions between groups were no homogeneous, which could be a source of bias. In contrast, the aim of our vestibular protocol is to achieve a standardize and homogeneous intervention to improve dizziness, balance, fatigue and quality of life in MS population.

Previous research of Hsu et al. [100] and Yeh et al. [31] based their VR experimental intervention on the Cawthorne-Cooksey protocol in non-MS patients with peripheral vestibular problems. Both authors apply the same own develop software in contraposition of commercial type exergames used in the current VRi protocol. Despite that own develop software is designed considering patients' needs and characteristics, commercial VR games have been reported in scientific research to be effective in MS [101]. Exergames of our protocol can be obtained costless by anyone while the mentioned software is not available to people outside the research. Also, our intervention only needs the "all in one" Oculus Quest HMD against the 3 virtual devices (Nintendo Wii, Microsoft Kinect and 3D glasses used by them. This restricts the possibility to get a portable device to implement a home-based or telerehabilitation program.

Owe to SARS-CoV-2, telerehabilitation strategies have been boosted in the last year [102], although this type of intervention joined to VR has been poorly studied in MS population [103]. A recent study of ten MS participants showed satisfactory results in balance and gait, but not for fatigue, after a telerehabilitation intervention based on Nintendo Wii exergames [104]. Regarding to our protocol, thanks that Oculus Quest is wireless and portable, exercises could be performed at laboratory, public or private clinic and at home. Additionally, this HMD have two features to secure safety. First one is a restricted game zone to avoid blows, and if you get out it, real physical context will be displayed on the headset. Second, the virtual content of the session could be supervised through the Oculus App or via streaming, which is essential in telerehabilitation or home-based program [105].

As conclusion, this pilot RCT protocol describes the first immersive virtual reality intervention based on a gold standard vestibular therapy addressed to MS population.

Declaration of conflicting interests.

Authors of this papers declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

CGM, MDCV and MJCH conceptualised and designed the study. CGM wrote the first draft of the manuscript with critical input from MJCH. MDCV, MJCH, JCHR, EPP and RPC contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

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FIGURES LENGEND

Figure 1: The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 2: Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc.

Table 1. Description of initial phase of vestibular intervention in both groups of study base on convectional protocol of Cawthorne- Cooksey exercises

Block of exercises	CG: Duration/ repetition	CG intervention: Cawthorne- Cooksey protocol	EG intervention: adaptation of Cawthorne-Cooksey protocol to **virtual environments**	EG: Duration/ repetition
Sit down: eyes and head movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetition	1. Stare a finger put in front of the face; move it closer and farther	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	27 minutes (combination of two blocks is performed because some exercises are answered by the same exergame) - Main room of First Steps: 11 minutes (10 slow repetitions and then 10 faster repetitions) - Shots in the Space: 7 minutes (all guns) - Beat saber:3 minutes (1 song)
		2. Move the head to the right and the left, with open eyes	**First Steps: Main room and Shots in the Space**. Move and object in front of eyes and follow it + Shooting targets that appeared in the exergame
		3. Move the head up and down, with open eyes	**Shots in the Space (First Steps).** Shooting target that appeared randomly inside the virtual environment
		4. Look up and down while the head is fixed	**Beat Saber + Main room of First Step.** Cutting blocks with saber while head is fixed / hit a ball in the main room and fixated gaze on its movement while head is fixed
		5. Look to the right and left while the head is fixed	
		6. Repeat exercise 4 and 5 in close eyes condition	Not possible in virtual environment
Sit down: head and body movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetition	1. Look an object placed in the floor. Then bring it above the head and place it again on the floor. Along all the movement look to the object.	**Main room of First Steps** Take a block from the virtual desk and bring to the floor and then above your head, while staring at it
		2. Shrink your shoulders and do circular movements	**Dance with Robot (First Steps)** Shrink shoulder while dancing with a Robot
		3. Bend forward and move an object around your knees	**Main room of First Steps** Bend forward and move a virtual block between the knees

Standing up exercises	15 minutes Each exercise will be performed 5 slow repetitions and then 5 faster repetition	1. Sit down and stand up and vice versa with open eyes	**Beat saber**	18 minutes - Beat sabe: 3 minutes (1 song) - Baseball: 8 minutes - Tennis: 4 minutes - Bowling: 6 minutes
		2. Sit down and stand up and vice versa with close eyes	Not possible in virtual environment	
		3. Stand up moving to the right while standing	**Bowling (Sports Scrambles)** Stand up moving to the right or the left while taking a bowling ball	
		4. Stand up moving to the left while standing		
		5. In front of your face, throw a ball from one hand to the other	**Baseball/ Tennis (Sports Scrambles)** Throw or hit al ball in front of your face	
		6. Under the knee level, throw a ball from one hand to the other	**Bowling (Sports Scrambles)** Throw the ball to hit the bowls under the knee level	

Table 2. Description of advanced phase of vestibular exercises for both groups

Exercises for both groups	CG: Duration and frequency	**Control group**	**Experimental group**	EG: Duration and frequency
1. Changing from sitting to standing and vice versa	10 repetitions	From a situation of sitting in a chair stand up and throw a ball	**Main room of First Steps** Take a block from virtual desk and when the subject stands up throw it a virtual sign situated inside the virtual environment	10 repetitions
2. Move and throw an object from one hand to the other while standing with feet together. Staring all the time to the object.	10 repetitions moving the object 10 repetitions throwing the object	Move a ball at eyes level and then throw it from one hand to the other	**Main room of First Steps** Move a virtual block at eyes level Take a virtual block and throw it from one hand to the other	10 repetitions moving the object 10 repetitions throwing the object
3. 360º turn	10 repetitions to the right 10 repetitions to the left	Turn 360º degrees and throw a ball to a target	**Main room of First Steps** Take a virtual block, turn 360 º and throw it to a located target in the environment	10 repetitions to the right 10 repetitions to the left
4. Moving the head with narrow base of support	15 repetitions (Example: 1 repetition look to the right)	Move head to right and left with feet together	**Main room of First Steps** In standing position with narrow base of support hit a ball and follow with the head its movements	5 repetitions (Example: 1 repetition is until the ball stops)
5. Stare an object put in front of the face; move it closer and farther while	10 slow repetitions 10 fast repetitions	Stare a small ball and move it closer or farther to your face	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	10 slow repetitions 10 fast repetitions

standing on foam surface				
6. Fast side head movements while standing on foam surface	15 repetitions	Throwing a ball to the right and left to the left while standing on a foam surface. Follow the ball with the head	**Main room of First Steps** Take the pin-pong racquet and hit blocks to one side and another following them with the head	15 repetitions
7. Move and object to the floor and bring it above your head while standing on a foam surface	10 repetitions	Taking a ball and make the exercise	**Main room of First Steps** Taking a virtual block from the desk perform the exercise	10 repetitions
8. Head movements while alternative single leg support	15 repetitions	Look to the right and the left while you maintain a monopodal balance	**Shots in the Space (First Steps)** Shooting targets just with one pistol, while single leg support	1 game
9. Head movements in a tandem position	15 repetitions	Look to one side and other while maintaining a tandem position	**Shots in the Space** Shooting targets with double gun while you maintain a tandem position	1 game
10. Head movements while standing on a foam surface	15 repetitions	Look to one side and other while standing on a foam surface	**Shots in the Space** Shooting targets with a machine gun while standing on a foam surface	1 game
11. Ocular movements with fixed head while standing on foam surface	20 repetitions (5 to right 5 to left 5 up 5 down)	Move eyes with fixed head while standing on a foam surface	**Beat Saber** Hit and cut blocks in a specific direction with sabers while standing on a foam surface	1 game
12. Throw a ball while standing on a foam surface	15 repetitions	Throw a ball to the physiotherapist and catch it again	**Baseball (Sports Scrambles)** Throw the ball in a baseball stadium while standing on a foam surface	1 game

13. Bowling with narrow base of support	10 repetitions	Bowl with feet together	**Bowling (Sports Scrambles)** Bowl with feet together	1 game
14. Bowling while standing on a foam surface	10 repetitions	Perform the exercise	**Bowling (Sports Scrambles)** Perform the exercise	1 game
15. Head movements while walking through a corridor	20 repetitions	Walk down a corridor while moving head	**Bowling (Sports Scrambles)** Walk down a bowling alley, while moving head side to side and the throw the bowling ball	2 games

Table 3. Data collection							
Data and outcomes of study	**Assessment details**	**Screening and recruitment**	**Baseline T0**	**During intervention**	**After intervention T1**	**Follow-up at 3 months T2**	**Follow-up at 6 months T3**
Eligibility assessment		X					
Demographic variables		X					
Feasibility	Usability: SUS Participation rate Retention rate Adherence rate				X		
Safety	Cybersickness: SSQ Falls/ adverse events registry			X	X		
Dizziness	DHI		X		X	X	X
Static Balance	Biodex Balance System: Length, antero-posterior, mediolateral sway and velocity of centre of pressure. Open and close eyes condition. Firm or foam surface.		X		X	X	X
Dynamic Balance	BBS		X		X	X	X
Fatigue	MFIS		X		X	X	X
Quality of life	MSQoL-54		X		X	X	X

DHI: Dizziness Handicap inventory; BBS: Berg Balance Scale; MFIS: Modified Fatigue Impact Scale; MSQoL-54: Multiple Sclerosis Quality of Life- 54; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

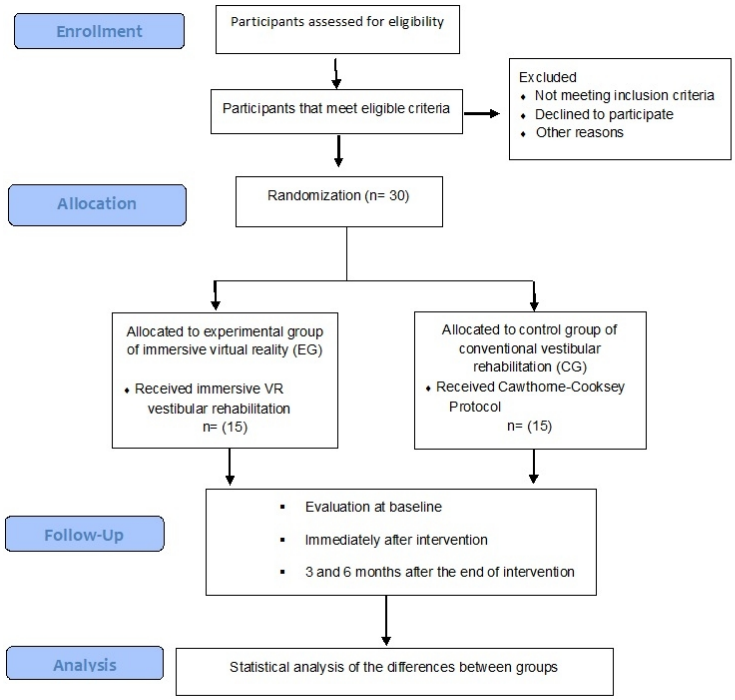

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

264x211mm (96 x 96 DPI)

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc.
1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

264x204mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7 + Table 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___9_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___10_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____10_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____8,10_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____10_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____10_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8,10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,5
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

ABSTRACT

Introduction

Vestibular impairments could explain dizziness, balance disorder, and fatigue in patients with multiple sclerosis (MS). Vestibular system damage may have a central and/or peripheral origin in this disease. Thus, the MS patient population could benefit from a vestibular rehabilitation program to improve these symptoms. As a successful tool in neurological rehabilitation, virtual reality (VR) can also be implemented within a vestibular rehabilitation intervention.

Methods and analysis

This protocol describes a parallel-arm, pilot randomised controlled trial (RCT), with blinded assessments, in 30 patients with MS with vestibular impairment (Dizziness Handicap Inventory > 16). The experimental group will receive an immersive virtual reality (VRi) vestibular rehabilitation intervention based on the Cawthorne-Cooksey vestibular rehabilitation protocol; the control group will perform the conventional protocol. Each group will receive a seven-weeks intervention (20 sessions, 3 sessions/week). The primary outcomes are the feasibility and safety of the vestibular VRi intervention in patients with MS. Secondary outcome measures are the changes in dizziness symptoms, balance performance, fatigue, and quality of life. Evaluations will be carried out at baseline, immediately after intervention, and after a follow-up period of 3 and 6 months.

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee, Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). Informed consent will be collected from participants who wish to participate in the research. The results of this research will be disseminated by using the literature in peer-reviewed scientific journals.

Trial registration number ClinicalTrials.gov NCT04497025.

Keywords: multiple sclerosis, vestibular diseases, dizziness, postural balance, fatigue, physical therapy modalities, virtual reality.

ARTICLE SUMMARY

Strengths and limitations of the study

- This study will address a relevant gap in MS research regarding the improvement of dizziness, balance, and fatigue in patients through the first VR vestibular training protocol.

- As the VRi intervention is developed and based on the Cawthorne-Cooksey conventional vestibular rehabilitation protocol, it allows a homogeneous comparison between study groups.
- The VRi systems offer multisensory feedback, oriented tasks, and repetitions of exercises in a ludic environment, overcoming the limitations of the Cawthorne-Cooksey vestibular protocol.
- Blinding of participants and therapists is not possible due to the type of intervention.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation, demyelination of the central nervous system, and axonal loss.[1,2] It affects more than 2.5 million people worldwide, and is one of the main non-traumatic causes of disability in young adults.[3–5] Balance disorders, dizziness, and fatigue are among the most common and troublesome symptoms in MS, repercussing on quality of life.[2,6–10] Fatigue is the most disabling manifestation in the study population, of which impairments in central sensory integration may be an underlying cause.[11,12] Likewise, vestibular symptoms such as vertigo, dizziness, and imbalance can enhance perceived fatigue.[13,14]

The affectation of the vestibular system is not only a notable problem in patients with MS, but could also be related to the progression of the disease.[15–18] There is a myriad of vestibular system disorders, which could have a peripheral (inner ear, vestibular nerve), central (brainstem and cerebellar), or combined source of damage.[18–20] Balance problems, lack of coordination in cephalic movement with regard to the body, ocular disturbances, and dizziness are symptoms related to vestibular system disorders, as well as MS[14,21–23] Postural deficits are associated with problems of the subjective visual vertical and dizziness during head movements, which are mediated by the vestibulo-ocular reflex (VOR).[21,24–26] Furthermore, impairments in the vestibulo-spinal reflex (VSR) can cause postural problems due to an inappropriate muscle response in imbalance situations.[26–30]. Central demyelination and/or peripheral disturbances can be possible aetiologies of vestibular impairments and their clinical manifestation in MS.[15,16,31,32] Patients with brainstem involvement identified in the Expanded Disability Status (EDSS) could be showing signs of balance, vestibular disorders, and greater disability.[33,34] Patients with MS could benefit from the goals of vestibular rehabilitation: decrease dizziness, improve ocular fixation, and improve stability, and its effect on daily living activities.[35–38]

Vestibular rehabilitation consists of exercises that provide accurate spatial information of the head with regard to body position while stimulating VOR, VSR, and somatosensory information.[7,36,39–41] Vestibular rehabilitation is based on mechanisms of substitution, adaptation, and habituation,[9,36] which appear to be helpful in both peripheral and central vestibular impairments.[31,42,43]

The effectiveness of conventional vestibular rehabilitation in improving dizziness, balance, and fatigue in patients with MS has recently been demonstrated in a meta-

analysis.[37] Although further research is needed, this meta-analysis reported that vestibular rehabilitation is more effective than no intervention and at least as effective as exercise-based interventions in any type of MS. Conversely, in the current scientific literature, there is an exponential growth in the number of studies that evaluate the usefulness of virtual reality (VR) applied to vestibular rehabilitation in other diseases.[44–52] The usefulness of non-immersive VR for balance and gait training has already been specifically proven in patients with MS.[53] Moreover, a recent review found that immersive virtual reality (VRi) can present added clinical benefits compared to conventional vestibular training.[54] The additional advantages of VRi compared to conventional vestibular exercises are performance and repetition of exercises in a motivational environment, oriented tasks, multisensory stimulation, extrinsic feedback, and promotion of patient adherence.[55–60] All of these stimulate neuroplastic changes in people with neurological affection as MS.[61] Within VRi, the modality of interventions that integrates physical activity in a virtual environment is exergames which has the aforementioned advantages and has proven to be effective for neurological diseases.[62,63] Moreover, despite exercising through a VR system, it is perceived as less exhausting.[64] Another remarkable benefit is the possibility of exposing a subject to a large variety of exposures, boosting the vestibular neuroplastic mechanism of habituation.[35,65] To the best of our knowledge, no previous research on VRi and vestibular rehabilitation in MS has been performed. VRi allows the subject to complete immersion within the 360º virtual environment, enhancing the feeling of presence.[66–68] Several authors, such as Meldrum et al.,[69] have declared the need to develop a standardised VR intervention protocol for vestibular rehabilitation and strengthen the evidence of the vestibular approach in the MS population.[70–72]

Therefore, we wish to develop a VRi vestibular protocol for MS. Thus, the primary purpose of this study is to determine the feasibility and safety of a VRi-based vestibular rehabilitation program in MS population. Second, we aim to preliminarily evaluate the effects of the vestibular VRi exercise protocol in comparison with conventional vestibular training for improvement in dizziness, balance, fatigue, and quality of life in patients with MS.

METHODS AND ANALYSIS

Study design

This protocol describes a two-arm parallel group design and a single-blinded pilot randomised clinical trial (RCT). To avoid bias during randomisation, the assessor will be blinded to group allocation. The future pilot RCT is a prospective study, with an initial evaluation of the sample before intervention, followed by an intervention period of 7 weeks. A further three evaluations will then be carried out immediately after intervention and after follow-up periods of 3 and 6 months. The study design is illustrated in Figure 1.

This protocol meets the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[73] This RCT will also be developed following instructions from the Consolidated Standards of Reporting Trials (CONSORT).[74] It has been registered at ClinicalTrials.gov with the identifier NCT04497025.

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Sevilla (Spain). The Virgen Macarena Hospital will be the main healthcare institution involved in this study. The inclusion of other healthcare centres in the area is expected.

Participants and recruitment

Recruitment of participants is expected to start in September 2021 and is estimated to be completed by September 2022. This will be carried out in the participants' healthcare institutions. The research team will begin by contacting the physical therapists and medical directors of each centre. All subjects that potentially meet the eligibility criteria will contacted and invited by phone to participate in the study. After providing oral and written information to the subjects, they will be free to decide if they wished to participate. Finally, people with MS who wish to participate in this study and meet the eligibility criteria will be asked for written informed consent (please see supplemental material for informed consent form).

Inclusion Criteria:

• Both male and female subjects aged 18-65 years

• Clinically diagnosed with any type of MS in accordance with the revised McDonald criteria. This will be assessed based on clinical history by a medical team.

• Walking ability according to the Expanded Disability Status Scale score (EDSS ≤ 6). This will be assessed based on clinical history by a medical team.

• Brainstem or cerebellar involvement with ≥ 2 points in the second functional system of the EDSS.[75] This will be evaluated based on clinical history by a medical team.

• Objective presence of dizziness symptoms (Dizziness Handicap Inventory (DHI) ≥ 16). This will be assessed after informed consent acceptance by an expert vestibular physical therapist.

• Objective presence of fatigue (Modified Fatigue Impact Scale (MFIS) ≥ 38)[76] or balance problems (Berg Balance Scale (BBS) ≤ 47).[77]. This will be evaluated after the acceptance of participation in the study by an expert vestibular physical therapist.

Exclusion Criteria:

• Partial or complete blindness

• Cognitive impairment (Mini-Mental State Examination score ≤ 24)

• Another neurologic disorder contributing to balance impairment

• Disease relapse within the last 3 months (transitory exacerbations of the disease by the appearance of neurological clinical manifestations imbalance, dizziness, and more)[15,78,79]

• Changes in MS pharmacotherapy within the last 3 months

• History of vestibular rehabilitation within the last 6 months

• Acute cardiovascular or respiratory illnesses

• Contraindications to VRi use (epilepsy, spatiotemporal disorientation, and cognitive impairment)

• Any other contraindications to physical activity

Exclusion criteria will be assessed based on clinic history by a medical team.

Randomisation, concealment allocation, and blinding

Participants will be randomly allocated to one of the two intervention groups by an independent researcher. We will consider a 1:1 distribution ratio and a computer-generated random sequence. The independent researcher will be in charge of the randomisation process and place the allocation of participants in sealed and concealed envelopes. This researcher will inform participants of their random allocation and will provide them the informed consent forms. An expert physical therapist in vestibular rehabilitation will perform the intervention. The assessor will remain blinded to the participants' groups.

Patient and public involvement

No patients or public are involved in designing the trial, but a number of public organisations have been contacted for patient recruitment (for example, Hospital Virgen Macarena, Ilustre Colegio Profesional de Fisioterapeutas de Andalucía). Once the results are published, participants will be informed about them by e-mail in an understandable writing; furthermore, the researchers will perform meetings in each public organisation engaged in recruitment.

Interventions

Conventional Vestibular Rehabilitation Protocol (CG)

The control group (CG) will perform the conventional vestibular rehabilitation Cawthorne-Cooksey protocol exercises, which have also been used to develop experimental interventions.[39] These exercises aim to restore balance affected by vestibular dysfunction or train the vestibular system. This improves vestibular compensation through a mechanism of neuroplasticity, known as adaptation, habituation, and substitution.[35,65,80] The primary goal of these mechanisms is to adapt the VOR and VSR, habituate and substitute head movements that provoke vestibular and balance symptoms, and train dynamic balance.

As shown in Table 1, exercises are divided into three blocks, which will be performed slowly at first and then faster. Participants allocated to the CG will receive this conventional protocol three times per week for 7 weeks. Each session will last for 50 min, and the rest time will be for at least 5 min. A total of 10 initial sessions and 10 advanced sessions will be carried out. Based on previous studies, during the initial phase, exercises of the first and second blocks will be carried out by 10 slow repetitions and 10 fast repetitions.[81,82] The third block exercises will be repeated five times slowly and then five times more quickly. The complete intervention time for each block is 15 min (Table 1). Once participants have exceeded the first ten sessions, they will begin with more complex exercises. To developed these advanced vestibular exercises for both groups, the principles and keys of Cawthorne-Cooksey,[39] Han et al..[35] and Whitney et al.[65] for this type of rehabilitation were assumed. The advanced phases of intervention for participants in the control group are described in Table 2. This intervention matches the experimental group (EG), with the only difference being that exercises are not performed in an immersive virtual environment. The exercise parameters in the advanced sessions described in order of difficulty within the session are the amplitude of the support base, alternative single leg support, tandem position, unstable surface, and walking while head movements. The inclusion of these parameters will be carried out in the aforementioned order to avoid the appearance of vestibular symptoms during the exercises. These parameters provide proprioceptive disturbances and encourage vestibular training through substitution of neural mechanisms.[35,65] Other parameters that train habituation and adaptation mechanisms include the increasing speed of head movement or its range of motion.[35,65] All parameters can be adapted to patient characteristics and progress with the session (for example, modifying the base of support from higher to lower amplitude on the firm and unstable surface).

The vestibular program will be conducted by an experienced vestibular rehabilitation physical therapist, who will provide verbal indications and stay near the participants to lend them confidence and decrease the risk of falling during the session.

Immersive Virtual Reality Intervention (EG)

Participants assigned to the EG will receive VRi vestibular rehabilitation through the head-mounted display (HMD) Oculus Quest. VRi allows complete immersion in a 360º virtual environment and enables interaction. Virtual immersive rehabilitation can only be achieved with the use of a VR headset or HMD. In this protocol, the new generation Oculus Quest equipment has been selected, which has some added advantages compared to other similar HMDs. These advantages include the absence of movement sensors or laptop installations, wireless option, portability, and a reduced risk of suffering from cybersickness syndrome, owing to the high resolution and accurate movement capture.[83,84]

To achieve homogeneous interventions over the two groups, the VRi intervention have been designed based on the gold standard Cawthorne-Cooksey vestibular protocol. Subjects in this group will receive the same number of sessions and duration as the CG. Similar to the CG, the first 10 sessions of the VRi treatment will be carried out in the sitting down position (eyes and head movement/head and body movement) and the last one as standing up exercises. The number of repetitions and adaptation of VRi equated to

the conventional protocol for immersive virtual environments during the initial phase are described in Table 1. In the initial phase, the advance phase exercises will be the same in both groups, with the main difference being the interaction with the immersive virtual environment. The advance phases of vestibular rehabilitation and the VRi-adapted exercises are shown in Table 2. The exercise parameters described in the CG will be applied in the EG as well. In addition, to prevent falls over interaction with virtual environments, participants will be monitored and supervised by an expert physical therapist.

First Steps, Beat Saber demo and Sport Scrambles demo games will be displayed in the Oculus Quest Virtual Glasses to apply the vestibular protocol. These games respond to a first-person exergame intervention in which subject actions are recreated simultaneously inside the virtual environment. Furthermore, all selected games are commercially available and have free access in the Oculus app to anyone who owns an HMD device. *First Steps* is the onset game of Oculus, in which one learns to use the VRi device in a playable way. This game consists of the *Main room* where the subject can interact with virtual objects as virtual blocks, pin-pong racket and ball, hanging ball, and more. It also contains two more virtual environments within the videogame. The first is a shooter game called *Shots in the Space*, which aims to reach the highest score while shooting random targets at a space station. This shooter is offersed three options: a single gun, a double gun, or a machine gun. The second is *Dance with Robot*, in which one dances and interacts with a robot following some indications. *Beat saber* is a rhythm music game in which blocks are slashed in a specific direction with a red (left hand) and blue (right hand) saber, while trying to avoid some obstacles. *Sport Scrambles* consist of three sports games: baseball, tennis, and bowling, in which one must defeat their opponent while balls, rackets, or your baseball bat are randomly changing into a giraffe, a cheese, and so on. The virtual scenarios are shown in Figure 2.

Outcomes and measurements

The primary outcomes will include the feasibility and safety of the experimental VRi vestibular protocol. The feasibility of the study will be assessed using recruitment,[85] adherence,[86] retention rates,[85] and usability of the VRi device.[87,88] Safety will be examined by the appearance of cybersickness[89] and fatigue to exercise[90] along the virtual reality treatment and a registry of falls and other adverse events. Pre-defined thresholds for considering the feasibility and safety of the VRi intervention are described in Table 3.

Secondary outcomes will drive to assess the changes in dizziness, balance, fatigue, and quality of life after a VRi vestibular protocol compared with conventional vestibular rehabilitation.

Usability of the Virtual Reality System

In combination with participation, retention, and adherence to treatment rates, feasibility will be evaluated using the System Usability Scale (SUS). The SUS is a 10-item

questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means 'strongly disagree' and 5 means 'strongly agree'. The overall score ranges from 0 to 100, which is obtained by multiplying the sum of every item by 2.5. A higher score indicates higher usability.[87,88] To maintain the blindness of the assessor, this measurement will be performed by the physiotherapist who conducted the intervention.

Cybersickness Syndrome

To assess the safety of the intervention along with the fall and adverse events registry, the appearance of cybersickness will be evaluated using the Simulator Sickness Questionnaire (SSQ). The SSQ is implemented to measure the appearance of sickness due to a virtual environment. The SSQ consists of a 16-item questionnaire divided into three categories: nausea, oculomotor, and disorientation.[91,92] Scores ranging between 10 and 15 indicate significant symptoms, and those above 20 indicate a simulator problem.[89] This scale will be provided by the physical therapist during each session.

Rating-of-Fatigue Scale

To examine safety along with the performance of the sessions, the appearance of fatigue related to exercise will be evaluated through Rating-of-Fatigue (ROF) [90]. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted). The main aim of this scale is to assess fatigue in myriad contexts while exercising or during daily living activities. The ROF will be presented to the participants in each session.

Dizziness

Dizziness symptoms will be assessed using the DHI. This self-assessment questionnaire consists of 25-items divided into the following subscales: physical, emotional, and functional. The physical and emotional subscales range from 0 to 36 points, and the functional subscale ranges from 0 to 28 points. The total score is 100, which relates to the highest level of disability and handicap.[93–95] This instrument is reliable and valid for the study population.[96,97] The minimal clinical importance difference (MCID) has been established at 18 points in patients with vestibular disorders.[95]

Balance

Static balance will be evaluated using the Biodex balance system. The aforementioned system allows the registration of the location of the centre of pressure (CoP).[98–100] Biodex has been proven to be a valid instrument for evaluating stability and postural control in subjects sith MS.[101, 102] Moreover, Biodex can compute the following variables in relation to the CoP:

- Length (mm), the CoP trajectory throughout the platform surface.

- Anteroposterior (SAP) and mediolateral sway (SMS); these measure CoP deviation along each axis (mm).
- Velocity (mm/s) of CoP oscillation through the anteroposterior axis (VAP) and mediolaterally (VML).

Each variable will be assessed in open or close eyes condition and firm or foam surface, respectively.

The BBS will be used to measure dynamic balance. The BBS consists of 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.[103,104] This assesses the skills of sitting, standing, leaning, turning, and standing on a monopodal support. The BBS has proved to be reliable and valid for the study population.[96,97] The MCID for BBS has been set at 3 points for people with MS by Gervasonni et al.[105]

Fatigue

The MFIS is a self-reported questionnaire that evaluates the perceived impact of fatigue in patients with MS. This scale is composed of 21 items which assess the fatigue impact in three different domains. The global scale is divided into 9, 10, and 2 items that belong to the physical, cognitive, and psychosocial domains, respectively. The total score is 84, with higher scores indicating a higher impact of fatigue.[106,107] This scale is reliable and valid for measuring the impact of fatigue in subjects with MS.[108,109] MCID for MFIS has been established at 19.23% by Rietberg et al.[110] and 4 points by Scott et al.[111]

Quality of Life

To assess the changes perceived by participants in their quality of life, the reliable and valid multiple sclerosis quality of life scale 54 (MSQoL-54) will be used.[112] This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score ranges from 0 to 100. Higher values indicate a better quality of life.[113]

Data will be collected by a blinded physical therapist who is an expert in neurological and vestibular rehabilitation. The blind evaluation will be performed at several points in the study: before the intervention, at the end of the intervention, and at 3 and 6 months post-intervention (Table 4).

Sample size calculation

A major reason for conducting a pilot study is to determine the initial data to perform a sample size calculation for a larger trial.[77] For this reason, the formal sample size is not calculated. However, following the recommendations of good practice for the design and analysis of feasibility and pilot studies in preparation for RCT,[77, 78] we aimed to recruit at least 30 subjects (15 per group).

Statistical analysis

To assess the feasibility and safety of the experimental VRi intervention, a descriptive data analysis will be implemented, taking into consideration the pre-defined thresholds for the primary outcomes (Table 3). Participants' flow will be analysed to report the proportion of subjects who are eligible, consenting, adhering to intervention, and have retention rates at 3 and 6 months. These data will help to identify possible modifications in the definitive trial design.

The normal distribution of the variables will be assessed using the Shapiro-Wilk test. For normal distribution, data will be reported as mean ± standard deviation or as percentages. Similarly, for non-normal distribution, median, minimum and maximum values, and interquartile ranges (IQR) will be reported. Baseline differences between groups will be analysed using the chi-square test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. This will help identify possible covariates.

Linear mixed models will be used to test group, time, and group-by-time interaction effects for all secondary variables. The analyses will be first unadjusted for any baseline characteristics and later adjusted for possible identified covariates (for example, gender or EDSS scores). An intention-to-treat approach will be used for data analysis.

Cohen´s criteria will be followed to assess the effect sizes of the studied variables, but due to the pilot nature of the study, all the effect analyses must be considered exploratory only. However, these data will help in sample size calculations in a definitive RCT. For all tests, $p < 0.05$ will be considered statistically significant. Graphical and numerical analysis of the data will be conducted using SPSS (version 25.0; IBM Corp, Armonk, NY, USA) and GraphPad PRISM (GraphPad Inc., San Diego, CA, USA).

Data management and monitoring

The research will not have an established data monitoring committee because the main decisions will be consensual between investigators. All data will be codified and recorded in an encrypted database by a number (in step of the subjects' name, for example) known only by the researcher team. The data will not be disclosed to third parties without participant consent.

Falls or any other adverse events derived during the intervention will be recorded by the therapists in a registry. These events will be communicated to the principal investigator of the study.

ETHICS AND DISSEMINATION

The study was approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). All participants will undergo and provide informed consent before data compilation. The investigators will disseminate the study results through literature in peer-reviewed scientific journals.

DISCUSSION

The current protocol for this pilot RCT aims to assess the feasibility and safety of vestibular rehabilitation in patients with MS through a VRi intervention compared with the conventional approach. Likewise, we will evaluate the changes that occurred in dizziness, postural control, fatigue, and quality of life for both study groups after the vestibular intervention.

Technical progress of VRi

Due to the intrinsic advantages of VRi and the multimodal design [114]of the protocol, the limitations of the Cawthorne-Cooksey training are expected to be overcome by providing extrinsic feedback (game score and multisensorial stimulation) during exercise execution, cognitive and task-oriented training (exergames), and avoiding humdrum exercise repetitions because of the motivational and enjoyable environment . [54,114]

Owing to VRi tracking (gyroscopes, accelerometers, and magnetometers) and software systems that record head and corporal movements in six degrees of freedom, it is possible to perform exercises in different postural circumstances, similar to our experimental protocol (sitting down, standing, single leg support, tandem, and standing on foam surface), ensuring virtual environment verticality.[84,115] Furthermore, the command centre of movements and multisensory stimulation are primarily found at the cephalic level in HMD, making VRi a suitable device for vestibular rehabilitation.[91,116–118] Moreover, current VRi devices are affordable, own high-resolution graphics, higher frames per second, less delay and latency, and accurate software and hardware.[119,120] These enhance the sense of presence and immersion of the subject and reduce the possible appearance of cybersickness, as confirmed by Weech et al.[121]

Clinical applicability of VRi vestibular rehabilitation

The Cawthorne-Cooksey intervention, on which our VRi protocol is based, has been demonstrated to be effective in several populations, such as elderly people,[114] people with vertebrobasilar insufficiency,[122] and those with benign paroxysmal positional vertigo.[123] Thus, it is expected that the vestibular VRi intervention based on this gold standard could be effective in the mentioned populations, in addition to MS. However, to confirm this statement, extensive research is needed. In contrast, previous studies have reported the effectiveness of VRi in vestibular rehabilitation for unilateral vestibular hypofunction,[48,50] Ménière disease,[45,46] and traumatic brain injury.[124] On the other hand, the recent systematic review by Soltani et al.[125] supports HMD as a feasible and safe intervention to improve balance in older adults; because of this, we expect that VRi vestibular intervention will be safe and feasible in MS population [71,126–128].

Finally, telerehabilitation strategies combined with VR have been poorly studied in the MS population.[129] A recent study with ten MS participants showed satisfactory results in balance and gait, but not for fatigue, after a telerehabilitation intervention based on Nintendo Wii exergames.[130] With regard to our protocol, because Oculus Quest is wireless and portable, exercises can be performed at the laboratory, in public, in private

clinics, and at home. In addition, this HMD has two features to ensure safety. The first is a restricted game zone to avoid blows, and on getting out, the real physical context will be displayed on the headset. Second, the virtual content of the session can be supervised through the Oculus app or via streaming, which is essential in telerehabilitation or home-based programs.[131]

In conclusion, this pilot RCT protocol describes the first immersive VR intervention based on a gold standard vestibular therapy for the MS population.

Declaration of conflicting interests.

Authors of this papers declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

CGM, MDCV and MJCH conceptualised and designed the study. CGM wrote the first draft of the manuscript with critical input from MJCH. MDCV, MJCH, JCHR, EPP and RPC contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

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FIGURES LENGEND

Figure 1: The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 2: Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc.

Table 1. Description of initial phase of vestibular intervention in both groups of study base on convectional protocol of Cawthorne- Cooksey exercises

Block of exercises	CG: Duration/ repetitions	CG intervention: Cawthorne- Cooksey protocol	EG intervention: adaptation of Cawthorne-Cooksey protocol to **virtual environments**	EG: Duration/ repetition
Sit down: eyes and head movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Stare a finger put in front of the face; move it closer and farther	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	27 minutes (combination of two blocks is performed because some exercises are answered by the same exergame) - Main room of First Steps: 11 minutes (10 slow repetitions and then 10 faster repetitions) - Shots in the Space: 7 minutes (all guns) - Beat saber:3 minutes (1 song)
		2. Move the head to the right and the left, with open eyes	**First Steps: Main room and Shots in the Space**. Move and object in front of eyes and follow it + Shooting targets that appeared in the exergame
		3. Move the head up and down, with open eyes	**Shots in the Space (First Steps).** Shooting target that appeared randomly inside the virtual environment
		4. Look up and down while the head is fixed	**Beat Saber + Main room of First Step.** Cutting blocks with saber while head is fixed / hit a ball in the main room and fixated gaze on its movement while head is fixed
		5. Look to the right and left while the head is fixed	
		6. Repeat exercise 4 and 5 in close eyes condition	Not possible in virtual environment
Sit down: head and body movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Look an object placed in the floor. Then bring it above the head and place it again on the floor. Along all the movement look to the object.	**Main room of First Steps** Take a block from the virtual desk and bring to the floor and then above your head, while staring at it
		2. Shrink your shoulders and do circular movements	**Dance with Robot (First Steps)** Shrink shoulder while dancing with a Robot
		3. Bend forward and move an object around your knees	**Main room of First Steps** Bend forward and move a virtual block between the knees

<table>
<tr><td rowspan="6">Standing up exercises</td><td rowspan="6">15 minutes

Each exercise will be performed 5 slow repetitions and then 5 faster repetitions</td><td>1. Sit down and stand up and vice versa with open eyes</td><td>Beat saber</td><td rowspan="6">18 minutes

- Beat sabe: 3 minutes (1 song)
- Baseball: 8 minutes
- Tennis: 4 minutes
- Bowling: 6 minutes</td></tr>
<tr><td>2. Sit down and stand up and vice versa with close eyes</td><td>Not possible in virtual environment</td></tr>
<tr><td>3. Stand up moving to the right while standing</td><td rowspan="2">Bowling (Sports Scrambles)
Stand up moving to the right or the left while taking a bowling ball</td></tr>
<tr><td>4. Stand up moving to the left while standing</td></tr>
<tr><td>5. In front of your face, throw a ball from one hand to the other</td><td>Baseball/ Tennis (Sports Scrambles)
Throw or hit al ball in front of your face</td></tr>
<tr><td>6. Under the knee level, throw a ball from one hand to the other</td><td>Bowling (Sports Scrambles)
Throw the ball to hit the bowls under the knee level</td></tr>
</table>

Table 2. Description of advanced phase of vestibular exercises for both groups

Exercises for both groups	CG: Duration and frequency	**Control group**	**Experimental group**	EG: Duration and frequency
1. Changing from sitting to standing and vice versa	10 repetitions	From a situation of sitting in a chair stand up and throw a ball	**Main room of First Steps** Take a block from virtual desk and when the subject stands up throw it a virtual sign situated inside the virtual environment	10 repetitions
2. Move and throw an object from one hand to the other while standing with feet together. Staring all the time to the object.	10 repetitions moving the object 10 repetitions throwing the object	Move a ball at eyes level and then throw it from one hand to the other	**Main room of First Steps** Move a virtual block at eyes level Take a virtual block and throw it from one hand to the other	10 repetitions moving the object 10 repetitions throwing the object
3. 360º turn	10 repetitions to the right 10 repetitions to the left	Turn 360º degrees and throw a ball to a target	**Main room of First Steps** Take a virtual block, turn 360 º and throw it to a located target in the environment	10 repetitions to the right 10 repetitions to the left
4. Moving the head with narrow base of support	15 repetitions (Example: 1 repetition look to the right)	Move head to right and left with feet together	**Main room of First Steps** In standing position with narrow base of support hit a ball and follow with the head its movements	5 repetitions (Example: 1 repetition is until the ball stops)
5. Stare an object put in front of the face; move it closer and farther while	10 slow repetitions 10 fast repetitions	Stare a small ball and move it closer or farther to your face	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	10 slow repetitions 10 fast repetitions

standing on foam surface				
6. Fast side head movements while standing on foam surface	15 repetitions	Throwing a ball to the right and left to the left while standing on a foam surface. Follow the ball with the head	**Main room of First Steps** Take the pin-pong racquet and hit blocks to one side and another following them with the head	15 repetitions
7. Move and object to the floor and bring it above your head while standing on a foam surface	10 repetitions	Taking a ball and make the exercise	**Main room of First Steps** Taking a virtual block from the desk perform the exercise	10 repetitions
8. Head movements while alternative single leg support	15 repetitions	Look to the right and the left while you maintain a monopodal balance	**Shots in the Space (First Steps)** Shooting targets just with one pistol, while single leg support	1 game
9. Head movements in a tandem position	15 repetitions	Look to one side and other while maintaining a tandem position	**Shots in the Space** Shooting targets with double gun while you maintain a tandem position	1 game
10. Head movements while standing on a foam surface	15 repetitions	Look to one side and other while standing on a foam surface	**Shots in the Space** Shooting targets with a machine gun while standing on a foam surface	1 game
11. Ocular movements with fixed head while standing on foam surface	20 repetitions (5 to right 5 to left 5 up 5 down)	Move eyes with fixed head while standing on a foam surface	**Beat Saber** Hit and cut blocks in a specific direction with sabers while standing on a foam surface	1 game
12. Throw a ball while standing on a foam surface	15 repetitions	Throw a ball to the physiotherapist and catch it again	**Baseball (Sports Scrambles)** Throw the ball in a baseball stadium while standing on a foam surface	1 game

13. Bowling with narrow base of support	10 repetitions	Bowl with feet together	**Bowling (Sports Scrambles)** Bowl with feet together	1 game
14. Bowling while standing on a foam surface	10 repetitions	Perform the exercise	**Bowling (Sports Scrambles)** Perform the exercise	1 game
15. Head movements while walking through a corridor	20 repetitions	Walk down a corridor while moving head	**Bowling (Sports Scrambles)** Walk down a bowling alley, while moving head side to side and the throw the bowling ball	2 games

Table 3. Primary outcomes pre-defined thresholds.		
Feasibility measurements	**Measure**	**Pre-defined thresholds**
Recruitment/participation rate [85]	Proportion of potential participants who agree to complete screening and consent to participate	≥65%
Adherence rate [86]	Proportion of participants who attend and complete the intervention	≥80%
Retention rate [85]	Proportion of participants with complete study data at 3 and 6 months follow-up	≥75%
Usability [87,88]	SUS	≥60 points
Safety measurements		
Cybersickness [89]	SSQ	≤ 15 points
Fatigue to exercise [90]	ROF	≤ 4 points
Adverse events	Session's registry	No between groups differences

ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

Table 4. Data collection							
Data and outcomes of study	**Assessment details**	**Screening and recruitment**	**Baseline T0**	**During intervention**	**After intervention T1**	**Follow-up at 3 months T2**	**Follow-up at 6 months T3**
Eligibility assessment		X					
Demographic variables		X					
Feasibility	Recruitment rate Adherence rate Retention rate Usability: SUS				X		
Safety	Cybersickness: SSQ Fatigue to exercise: ROF Falls/ adverse events registry			X			
Dizziness	DHI		X		X	X	X
Static Balance	Biodex Balance System: Length, antero-posterior, mediolateral sway, and velocity of centre of pressure. Open and close eyes condition. Firm or foam surface.		X		X	X	X
Dynamic Balance	BBS		X		X	X	X
Fatigue	MFIS		X		X	X	X
Quality of life	MSQoL-54		X		X	X	X

DHI: Dizziness Handicap inventory; BBS: Berg Balance Scale; MFIS: Modified Fatigue Impact Scale; MSQoL-54: Multiple Sclerosis Quality of Life- 54; ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

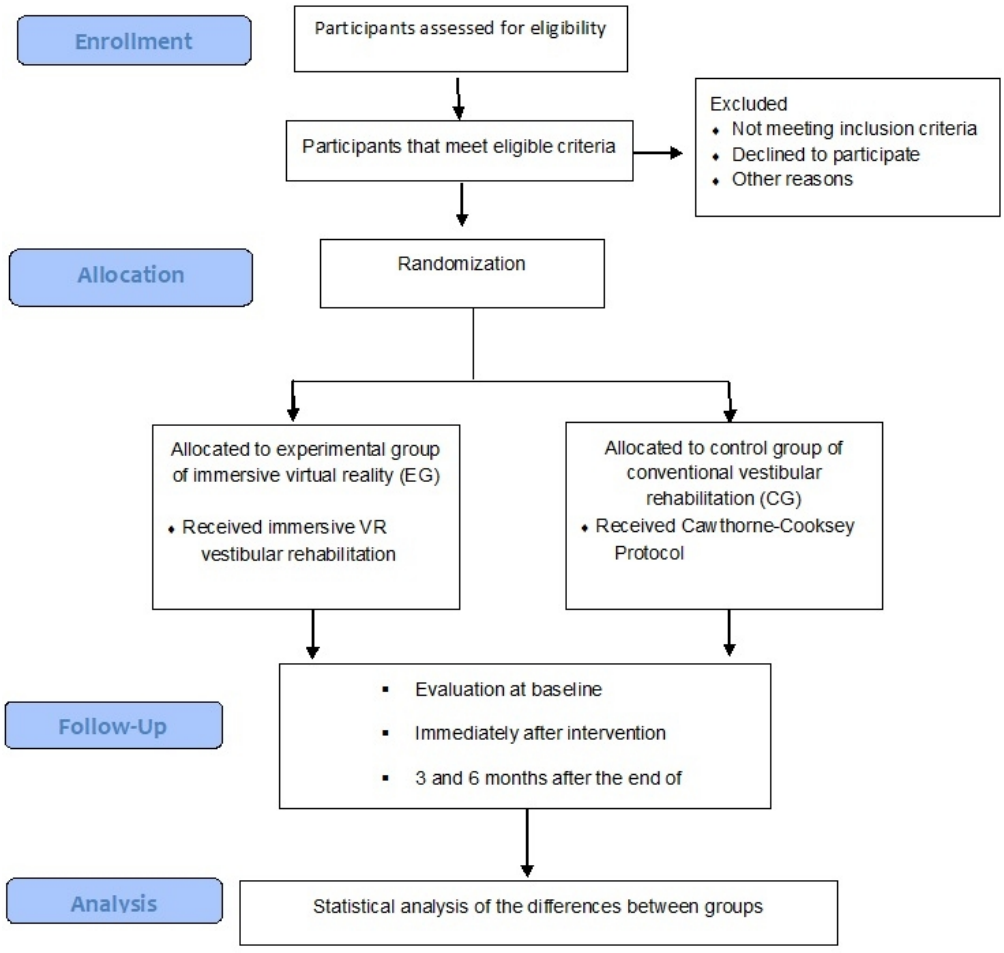

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 1: The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

193x211mm (96 x 96 DPI)

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc.
1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

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Model Informed Consent Form

Study Title*:* **Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial**

Principal investigator: Cristina García Muñoz

Organization: University of Seville

This informed consent is formed by two parts:

I. **Information sheet**
II. **Certificate of Consent**

A copy of this form will be provided to you, in order you can take as much time as you need to make the final decision.

Part I: Information sheet

A. Introduction

This informed consent form is for people with multiple sclerosis who suffer from dizziness, vertigo or imbalance. We are inviting you to participate in the research driven by our research team at the Physical therapy Department of the University of Seville (Spain). The current research was reviewed and approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). This study complies with the Helsinki Statement. The aim of this form is to provide you with enough information to help you in your participation decision. Please, before you decide, read the information below carefully and feel free to ask the investigator if you have any question. The information will help you to understand the objective of study, procedures and duration and the possible benefits or risk derived from the research.

B. Background

Dizziness, balance disorders and fatigue are common clinical manifestation in multiple sclerosis (MS) having a direct impact in quality of life. Dizziness could affect between of 49-59 % of MS patients, and it is highly related to imbalance. This problem could have a peripheral or central vestibular origin in this population. Thus, MS population could be benefit from a vestibular rehabilitation program. Major goals of vestibular rehabilitation are to decrease symptoms of dizziness, improve ocular fixation, improve stability and its effects on daily living activities. Immersive virtual reality (VRi) is a booming tool in vestibular and neurorehabilitation because of its added advantages. However, VRi has obtained promising results reducing dizziness and improving balance in patients with peripheral vestibular disorders, no previous studies can be found in MS. That is why it is necessary to examine the feasibility and safety of the VRi as a vestibular rehabilitation intervention to improve dizziness, balance, fatigue, and quality of life in people with multiple sclerosis. Both groups of study will receive the same intervention with the only difference of the performance of the exercises trough the VRi device. This study purposes a VRi intervention based on the gold standard vestibular protocol Cawthorne-Cooksey. Improvements of symptoms will have a direct repercussion in the quality of life of MS

patients. To examine these effects, up to 30 participants may join the experimental intervention purpose in this research applying a seven week intervention period.

C. Purpose of study

To assess feasibility and safety of the experimental VRi vestibular protocol.

To examine the changes in dizziness, balance, fatigue and quality of life after a VRi vestibular protocol compared to conventional vestibular rehabilitation.

Procedure

Your participation in this research is completely voluntary. Experimental intervention will not have any cost to you. If you decide to reject your participation, once you have singed the informed consent form, you are entirely free to do it. You only must notify your desire to the principal investigator. You will not be required to give reasons for your decision to leave the research process. No ethics or economics conflicts will be carried out because of your rejection to participate. If you are willing to participate, before you enrolled the study you need to sing this informed consent form. Before you start with therapy you will participate in a baseline assessment drive by a physical therapist trained in vestibular rehabilitation. This initial evaluation will take place at Physiotherapy Department of the University of Seville. This initial assessment is constituted by:

- Dizziness Handicap Inventory (DHI): is a self-assessment questionnaire of 25 items. The aim of DHI is to evaluate the impact of dizziness on the quality of life. Higher scores of the questionnaire means more impact of dizziness in quality of life.
- Static balance will be evaluated by the Biodex Balance System. The mentioned balance system allows registration of the location of the centre of pressure.
- The Berg Balance Scale (BBS) is the selected instrument to measure dynamic balance. BBS is constituted by 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.
- Modified Fatigue Impact Scale (MFIS): self-reported questionnaire that evaluates the perceived impact of fatigue in MS patients. This scale is composed of 21-items which assess fatigue impact in three different domains.
- Multiple Sclerosis Quality of Life Scale 54 (MSQoL-54): This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score range is from 0 to 100 scales. Higher values indicate better quality of life

Once the baseline assessment ends, vestibular rehabilitation will be administered by a qualified physical therapist.

During sessions, physical therapist will be near to you to avoid possible falls. If any falls or another adverse event occurs during session it will be register by the therapist. To assess the possible appearance of Cybersicknes (nausea, dizziness, vomitus due to the VRi) Simulator Sickness Questionnaire will be provided to you by the therapist.

- Simulator Sickness Questionnaire (SSQ): The SSQ consists of a 16-item questionnaire divided into 3 categories: nausea, oculomotor and disorientation. Scores ranging between 10 and 15 mean significant symptoms, and above 20 indicates a simulator problem.

- Rating-of-Fatigue Scale (ROF): It is employed to quantify fatigue during the performance of exercise. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted).

Once the intervention ends you will return to the University of Seville for a post-intervention revaluation in which same test and questionnaires will be provided to you. Only System Usability Scale will be new in the evaluation process.

- System Usability Scale (SUS): SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means strongly disagree and 5 means strongly agree. The overall score can range from 0 to 100.

A reassessment 3 and 6 month after the end of the intervention will be carried out at the University.

D. Study design

This study is a randomised control clinical trial in which is compared two different interventions each one in a defined group. The participants' allocation will be randomised into experimental group and control group. Evaluators will be blinded to intervention and group assignation; this is known as single-blind. Both groups will receive a total of 20 session based on gold standard protocol of Cawthorne-Cooksey. Is necessary to compare an immersive virtual reality intervention (VRi) to Cawthorne-Cooksey to know the real effects and possible benefits associated to virtual reality. Specialist vestibular physical therapist will monitor and supervise sessions.

- Control group intervention: Gradual exposition to vestibular exercises will be provided by 10 initial session and 10 advanced. Each session will last 50 minutes with 5 minutes of rest at the middle of the session. Session will be performed 3 times per week along 7 weeks. Vestibular exercises will be the same in both groups based on the conventional Cawthorne-Cooksey vestibular training.
- Experimental group: Same frequency and duration of intervention will be carried out in the experimental group. Also, vestibular exercises based on Cawthorne-Cooksey will be the same in both groups. The main difference in the experimental groups consist of the performance of exercises through the Oculus Quest system. Oculus Quest is a head mounted display through you can interact with a virtual reality environment. Exercises will be adapted to be execute in the virtual environment provided by exergames called: *First Steps*, *Beat Saber* and *Sport Scrambles*. Exergames can be defined as the videogame which allows to reproduce immediately external actions of the subject to the virtual world.

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E. Duration

The study starts at baseline assessment followed by administration of 20 session along 7 weeks. Once the intervention ends: DHI, Biodex Balance System, BBS, MFIS, MSQoL-54 VDAL, and SUS will be assessed and filled once more to examine the possible changes of outcomes. Reassessment will be made 3 and 6 months after the end of intervention.

We will ask you to meet you at the University, 4 times in total owe to the evaluation process. Your participation in the research take place over 9 months in total.

F. Benefits

After the experimental intervention dizziness, balance, fatigue, and quality of life may improve or be resolved.

Risks

The participation on this study may involve the following risk:

- Possible apparition of pain in extremities derived from the physical exercise
- Slight possibility of transient nausea or dizziness
- Appearance of cybersickness during the performance of exercises through Oculus Quest.
- Possible falls. To reduce this possibility your participation will be supervised by the physical therapist.

G. Reminders and responsibilities

- Notify the research team if you wish to leave the study
- Follow the instructions given by investigators to achieve homogeneous course of the intervention
- Ask investigators if you any doubt or you do not understand something
- Tell investigators if you experience health changes during the research

H. Confidentiality

The information collect from the study will be kept confidential. Considering to data protection law you can modified or deny the access to them getting in touch to the principal investigator. Your personal data (name, age, address…) will be registered in a database in the Spanish Data Protection Agency. All your data will be codified by a number (in step of your name for example) known only by researchers. The research team is the only one authorized to manage your personal data through a confidential password. Your data will not be disclosed to third parties without your consent.

I. Sharing the results

Results from the study will be share in Scientifics conference or meetings. Furthermore, the study results will be disseminated via publication in peer-reviewed scientific journals. Private or confidential information will not be published or shared.

J. Conflict of interest

Authors of this paper declared no potential conflicts of interest respect to the research. The research team only is interested in completing this study. The investigators interest should not affect your consideration for participating.

K. Right to Refuse or Withdraw

This is a reconfirmation that you are completely free to accept or decline the offer to participate in this study. Also, you are entirely free to leave the research at any point without giving reasons.

L. Questions about the study

If you have any questions or doubts about the research (before, during or after the study) or you would like to speak to the research team, please contact to the main investigator: physical therapist Cristina García (+34) 954 55 14 71.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand that I am entirely free to leave the study at any moment after informing the principal investigator. I promised to follow the team research indications as much as possible. I know the possible benefits or risk derived from the experimental intervention. A signed and dated copy of the informed consent form will be given to me. I agree voluntarily to participate as a participant in the research titled: Feasibility of an immersive virtual reality-based vestibular rehabilitation program for dizziness, balance, and fatigue improvement in people with multiple sclerosis: pilot randomised controlled study

Patient signature: _____ Date: _____

I have provided a detailed information of the study to the participant including the possible benefits and risks. I have witnessed the accurate reading of the consent form to the potential participant. I have answered all doubts of the participant related to the research. I confirm that the individual has given consent freely.

Investigator signature: _____ Date: _____

Decline participation

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand that I am entirely free to leave the study at any moment after informing the principal investigator. Although, I refuse to participate in the research proposed in this informed consent form.

Patient signature: _____ Date: _____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,13
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4,5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8 + Table 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_Table 3,10____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_Table 3, 8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____6_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___6_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___6_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___6_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___8,10_____ __
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__8_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___11_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___11_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____n/a_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____11_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____n/a_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____8,11_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____n/a_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____11_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,11
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

ABSTRACT

Introduction

Vestibular system damage may have a central and/or peripheral origin in multiple sclerosis (MS). Vestibular impairments may contribute to dizziness, balance disorders, and fatigue in patients with MS. Thus, the MS patient population could benefit from a vestibular rehabilitation program to improve these symptoms. As a successful tool in neurological rehabilitation, virtual reality (VR) can also be implemented within a vestibular rehabilitation intervention, also the immersive VR has demonstrated to be effective in peripheral vestibular problems in previous surveys.

Methods and analysis

This protocol describes a parallel-arm, pilot randomised controlled trial (RCT), with blinded assessments, in 30 patients with MS with vestibular impairment (Dizziness Handicap Inventory ≥ 16). The experimental group will receive an immersive virtual reality (VRi) vestibular rehabilitation intervention based on the conventional Cawthorne-Cooksey protocol; the control group will perform the conventional protocol. Each group will receive a seven-week intervention (20 sessions, 3 sessions/week). The primary outcomes are the feasibility and safety of the vestibular VRi intervention in patients with MS. Secondary outcome measures are the changes in dizziness symptoms, balance performance, fatigue, and quality of life. Evaluations will be carried out at baseline, immediately after intervention, and after a follow-up period of 3 and 6 months.

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee, Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). Informed consent will be collected from participants who wish to participate in the research. The results of this research will be disseminated by using the literature in peer-reviewed scientific journals.

Trial registration number ClinicalTrials.gov NCT04497025.

Keywords: multiple sclerosis, vestibular diseases, dizziness, postural balance, fatigue, physical therapy modalities, virtual reality.

ARTICLE SUMMARY

Strengths and limitations of the study

- As the VRi intervention is developed and based on the Cawthorne-Cooksey conventional vestibular rehabilitation protocol, it allows a homogeneous comparison between study groups.

- The VRi systems offer multisensory feedback, oriented tasks, and repetitions of exercises in a ludic environment, overcoming the limitations of the Cawthorne-Cooksey vestibular protocol.
- Blinding of participants and therapists is not possible due to the type of intervention.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation, demyelination of the central nervous system, and axonal loss.[1,2] Balance disorders, dizziness, and fatigue are among the most common and troublesome symptoms in MS, repercussing on quality of life.[2–7] Fatigue is the most disabling in MS, of which impairments in central sensory integration may be an underlying cause [8,9], also it can be enhanced by vestibular symptoms such as vertigo, dizziness, and imbalance. [10,11]

The affectation of the vestibular system is remarkable problem in MS that could be related to its progression.[12–15] There are a myriad of vestibular system disorders, which could have a peripheral (inner ear, vestibular nerve), central (brainstem and cerebellar), or combination.[15–17] Balance problems, lack of coordination in cephalic movement with regard to the body, ocular disturbances, and dizziness are symptoms related to vestibular disorders, as well as MS. [11,18–20] Postural deficits are associated with problems of the subjective visual vertical and dizziness during head movements, which are mediated by the vestibulo-ocular reflex (VOR).[18,21–23] Furthermore, impairments in the vestibulo-spinal reflex (VSR) can cause postural problems due to an inappropriate muscle response in imbalance situations.[23–27]. Central demyelination and/or peripheral disturbances can be possible aetiologies of vestibular impairments and their clinical manifestation in MS.[12–14,28] Patients with brainstem involvement identified in the Expanded Disability Status (EDSS) could be showing signs of imbalance, vestibular disorders, and greater disability.[29,30] MS Patients could benefit from goals of vestibular rehabilitation: decrease dizziness and improve ocular fixation, stability, and performance on daily living activities.[31–34]

Vestibular rehabilitation consists of exercises that provide accurate spatial information of the head with regard to body position whilst stimulating VOR, VSR, and somatosensory information.[4,32,35–37] This is based on mechanisms of substitution, adaptation, and habituation,[6,32] which appear to be helpful in peripheral and central vestibular impairments.[14,38,39]

Although further research is needed, conventional vestibular training has been reported as superior than no intervention and at least as effective than exercise-based approach for improving dizziness, balance and fatigue in any MS type. [33] Currently, there is an exponential growth of studies that evaluate the usefulness of virtual reality (VR) applied to vestibular rehabilitation in other diseases.[40–48] The usefulness of non-immersive VR for balance and gait training has been already proven in MS.[49] Moreover, a systematic review found that immersive virtual reality (VRi) presents added clinical benefits compared to conventional vestibular training (performance and repetition of exercises in a motivational environment, oriented tasks, multisensory stimulation,

extrinsic feedback, and promotion of adherence).[50–55] These stimulate neuroplastic changes in neurological affection as MS.[56] Within VRi, the modality that integrates physical activity in a virtual environment with mentioned advantages is exergame, that has proven to be effective for neurological diseases.[57,58] Moreover, despite exercising through a VR system, it is perceived as less exhausting [59], whilst the subject is expose to a large variety of environments boosting the vestibular mechanism of habituation. [31,60] VRi allows the subject to complete immersion within the 360º virtual environment, enhancing the feeling of presence.[61–63] To the best of our knowledge, no previous research on VRi and vestibular rehabilitation in MS has been performed. Authors as Meldrum et al.,[64] have declared the need to develop a standardised VR intervention protocol for vestibular rehabilitation and strengthen the evidence of this approach in the MS.[65–67]

Therefore, we wish to develop a VRi vestibular protocol for MS. Thus, the primary purpose of this study is to determine the feasibility and safety of a VRi-based vestibular rehabilitation program in MS population. Second, we aim to preliminarily evaluate the effects of the vestibular VRi exercise protocol in comparison with conventional vestibular training for improvement in dizziness, balance, fatigue, and quality of life in patients with MS.

METHODS AND ANALYSIS

Study design

This protocol describes a two-arm parallel group design and a single-blinded pilot randomised clinical trial (RCT). To avoid bias during randomisation, the assessor will be blinded to group allocation. The future pilot RCT is a prospective study, with an initial evaluation of the sample before intervention, followed by an intervention period of 7 weeks. A further three evaluations will then be carried out immediately after intervention and after follow-up periods of 3 and 6 months. The study design is illustrated in Figure 1.

This protocol meets the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[68] This RCT will also be developed following instructions from the Consolidated Standards of Reporting Trials (CONSORT).[69] It has been registered at ClinicalTrials.gov with the identifier NCT04497025.

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Sevilla (Spain). The Virgen Macarena Hospital will be the main healthcare institution involved in this study. The inclusion of other healthcare centres in the area is expected.

Participants and recruitment

Recruitment of participants is expected to start in September 2021 and end in September 2022. The research team will begin by contacting the physical therapist and medical directors of the participants' healthcare institutions. All subjects that potentially meet the eligibility criteria will be contacted and invited by phone to participate in the study. Those

who freely decide to participate and meet the eligibility criteria will be asked for written informed consent (please see supplemental material for informed consent form).

Inclusion Criteria:

• Both male and female subjects aged 18-65 years

• Clinically diagnosed with any type of MS in accordance with the revised McDonald criteria. This will be assessed based on clinical history by a medical team.

• Walking ability according to the Expanded Disability Status Scale score (EDSS ≤ 6). This will be assessed based on clinical history by a medical team.

• Brainstem or cerebellar involvement with ≥ 2 points in the second functional system of the EDSS.[70] This will be evaluated based on clinical history by a medical team.

• Objective presence of dizziness symptoms (Dizziness Handicap Inventory (DHI) ≥ 16). This will be assessed after informed consent acceptance by an expert vestibular physical therapist.

• Presence of fatigue (Modified Fatigue Impact Scale (MFIS) ≥ 38)[71] or balance problems (Berg Balance Scale (BBS) ≤ 47).[72]. This will be evaluated after the acceptance of participation in the study by an expert vestibular physical therapist.

Exclusion Criteria:

• Partial or complete blindness

• Cognitive impairment (Mini-Mental State Examination score ≤ 24)

• Another neurologic disorder contributing to balance impairment

• Disease relapse within the last 3 months (transitory exacerbations of the disease by the appearance of neurological clinical manifestations imbalance, dizziness, and more)[12,73,74]

• Changes in MS pharmacotherapy within the last 3 months

• History of vestibular rehabilitation within the last 6 months

• Acute cardiovascular or respiratory illnesses

• Contraindications to VRi use (epilepsy, spatiotemporal disorientation, and cognitive impairment)

• Any other contraindications to physical activity

Exclusion criteria will be assessed based on clinic history by a medical team.

Randomisation, concealment allocation, and blinding

Participants will be randomly allocated to one of the two intervention groups by an independent researcher. We will consider a 1:1 distribution ratio and a computer-

generated random sequence. The independent researcher will be in charge of the randomisation process and place the allocation of participants in sealed and concealed envelopes. This researcher will inform participants of their random allocation and will provide them the informed consent forms. An expert physical therapist in vestibular rehabilitation will perform the intervention. The assessor will remain blinded to the participants' groups.

Patient and public involvement

No patients or public are involved in designing the trial, but a number of public organisations have been contacted for patient recruitment (for example, Hospital Virgen Macarena, Ilustre Colegio Profesional de Fisioterapeutas de Andalucía). Participants will play a significant role in remodelling the intervention and to adapt it for the need of MS patients. It will be possible through a qualitative assessment of the experimental VRi vestibular training, performed through the semi-structured interview process for each participant. Once the results are published, participants will be informed about it by e-mail in a comprehensible writing style; furthermore, the researchers will perform meetings in each public organisation engaged in recruitment.

Interventions

Conventional Vestibular Rehabilitation Protocol (CG)

The control group (CG) will perform the conventional vestibular rehabilitation Cawthorne-Cooksey protocol exercises, which have also been used to develop experimental interventions.[35] These exercises aim to restore balance affected by vestibular dysfunction or train the vestibular system. This improves vestibular compensation through a mechanism of neuroplasticity, known as adaptation, habituation, and substitution.[31,60,75] The primary goal of these mechanisms is to adapt the VOR and VSR, habituate and substitute head movements that provoke vestibular and balance symptoms, and train dynamic balance.

As shown in Table 1, exercises are divided into three blocks, which will be performed slowly at first and then faster. Participants allocated to the CG will receive this conventional protocol three times per week for 7 weeks. Each session will last for 50 min, and the rest time will be for at least 5 min. A total of 10 initial sessions and 10 advanced sessions will be carried out. Based on previous studies, during the initial phase, exercises of the first and second blocks will be carried out by 10 slow repetitions and 10 fast repetitions.[76,77] The third block exercises will be repeated five times slowly and then five times more quickly. The complete intervention time for each block is 15 min (Table 1). Once participants have exceeded the first ten sessions, they will begin with more complex exercises. To developed these advanced vestibular exercises for both groups, the principles and keys of Cawthorne-Cooksey,[35] Han et al..[31] and Whitney et al.[60] for this type of rehabilitation were assumed. The advanced phases of intervention for participants in the control group are described in Table 2. This intervention matches the experimental group (EG), with the only difference being that exercises are not performed

in an immersive virtual environment. The exercise parameters in the advanced sessions described in order of difficulty within the session are the amplitude of the support base, alternative single leg support, tandem position, unstable surface, and walking while head movements. The inclusion of these parameters will be carried out in the aforementioned order to avoid the appearance of vestibular symptoms during the exercises. These parameters provide proprioceptive disturbances and encourage vestibular training through substitution of neural mechanisms.[31,60] Other parameters that train habituation and adaptation mechanisms include the increasing speed of head movement or its range of motion.[31,60] All parameters can be adapted to patient characteristics and progress with the session (for example, modifying the base of support from higher to lower amplitude on the firm and unstable surface).

The vestibular program will be conducted by an experienced vestibular rehabilitation physical therapist, who will provide verbal indications and stay near the participants to lend them confidence and decrease the risk of falling during the session.

Immersive Virtual Reality Intervention (EG)

Participants assigned to the EG will receive VRi vestibular rehabilitation through the head-mounted display (HMD) Oculus Quest. VRi allows complete immersion in a 360º virtual environment and enables interaction. Virtual immersive rehabilitation can only be achieved with the use of a VR headset or HMD. In this protocol, the new generation Oculus Quest equipment has been selected, which has some added advantages compared to other similar HMDs. These advantages include the absence of movement sensors or laptop installations, wireless option, portability, and a reduced risk of suffering from cybersickness syndrome, owing to the high resolution and accurate movement capture.[78,79]

To achieve homogeneous interventions over the two groups, the VRi intervention have been designed based on the gold standard Cawthorne-Cooksey vestibular protocol. Subjects in this group will receive the same number of sessions and duration as the CG. Similar to the CG, the first 10 sessions of the VRi treatment will be carried out in the sitting down position (eyes and head movement/head and body movement) and the last one as standing up exercises. The number of repetitions and adaptation of VRi equated to the conventional protocol for immersive virtual environments during the initial phase are described in Table 1. In the initial phase, the advance phase exercises will be the same in both groups, with the main difference being the interaction with the immersive virtual environment. The advance phases of vestibular rehabilitation and the VRi-adapted exercises are shown in Table 2. The exercise parameters described in the CG will be applied in the EG as well. In addition, to prevent falls over interaction with virtual environments, participants will be monitored and supervised by an expert physical therapist.

First Steps, Beat Saber demo and Sport Scrambles demo games will be displayed in the Oculus Quest Virtual Glasses to apply the vestibular protocol. These games respond to a first-person exergame intervention in which subject actions are recreated simultaneously inside the virtual environment. Furthermore, all selected games are commercially available and have free access in the Oculus app to anyone who owns an HMD device. *First Steps* is the onset game of Oculus, in which one learns to use the VRi device in a

playable way. This game consists of the *Main room* where the subject can interact with virtual objects as virtual blocks, pin-pong racket and ball, hanging ball, and more. It also contains two more virtual environments within the videogame. The first is a shooter game called *Shots in the Space*, which aims to reach the highest score while shooting random targets at a space station. This shooter is offersed three options: a single gun, a double gun, or a machine gun. The second is *Dance with Robot*, in which one dances and interacts with a robot following some indications. *Beat saber* is a rhythm music game in which blocks are slashed in a specific direction with a red (left hand) and blue (right hand) saber, while trying to avoid some obstacles. *Sport Scrambles* consist of three sports games: baseball, tennis, and bowling, in which one must defeat their opponent while balls, rackets, or your baseball bat are randomly changing into a giraffe, a cheese, and so on. The virtual scenarios are shown in Figure 2.

Outcomes and measurements

The primary outcomes will include the feasibility and safety of the experimental VRi vestibular protocol. The feasibility of the study will be assessed using recruitment, adherence, retention rates, and usability of the VRi device. In addition to quantitative assessment, qualitative data will be recorded through semi-structured interview process. This qualitative strategy allows to know main participants' perceptions of the VRi intervention received. Safety will be examined by the appearance of cybersickness and fatigue to exercise along the virtual reality treatment and a registry of falls and other adverse events. Pre-defined thresholds for considering the feasibility and safety of the VRi intervention are described in Table 3. [80–85] [80] [81] [82] [83] [84] [85]

Secondary outcomes will drive to assess the changes in dizziness, balance, fatigue, and quality of life after a VRi vestibular protocol compared with conventional vestibular rehabilitation.

Usability of the Virtual Reality System

In combination with participation, retention, and adherence to treatment rates, feasibility will be evaluated using the System Usability Scale (SUS). The SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means 'strongly disagree' and 5 means 'strongly agree'. The overall score ranges from 0 to 100, which is obtained by multiplying the sum of every item by 2.5. A higher score indicates higher usability.[82,83] To maintain the blindness of the assessor, this measurement will be performed by the physiotherapist who conducted the intervention.

Cybersickness Syndrome

To assess the safety of the intervention along with the fall and adverse events registry, the appearance of cybersickness will be evaluated using the Simulator Sickness Questionnaire (SSQ). The SSQ is implemented to measure the appearance of sickness

due to a virtual environment. The SSQ consists of a 16-item questionnaire divided into three categories: nausea, oculomotor, and disorientation.[86,87] Scores ranging between 10 and 15 indicate significant symptoms, and those above 20 indicate a simulator problem.[84] This scale will be provided by the physical therapist during each session.

Rating-of-Fatigue Scale

To examine safety along with the performance of the sessions, the appearance of fatigue related to exercise will be evaluated through Rating-of-Fatigue (ROF) [85]. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted). The main aim of this scale is to assess fatigue in myriad contexts while exercising or during daily living activities. The ROF will be presented to the participants in each session.

Dizziness

Dizziness symptoms will be assessed using the DHI. This self-assessment questionnaire consists of 25-items divided into the following subscales: physical, emotional, and functional. The physical and emotional subscales range from 0 to 36 points, and the functional subscale ranges from 0 to 28 points. The total score is 100, which relates to the highest level of disability and handicap.[88–90] This instrument is reliable and valid for the study population.[91,92] The minimal clinical importance difference (MCID) has been established at 18 points in patients with vestibular disorders.[90]

Balance

Static balance will be evaluated using the Biodex balance system. The aforementioned system allows the registration of the location of the centre of pressure (CoP).[93–95] Biodex has been proven to be a valid instrument for evaluating stability and postural control in subjects sith MS. [96,97] Moreover, Biodex can compute the following variables in relation to the CoP:

- Length (mm), the CoP trajectory throughout the platform surface.
- Anteroposterior (SAP) and mediolateral sway (SMS); these measure CoP deviation along each axis (mm).
- Velocity (mm/s) of CoP oscillation through the anteroposterior axis (VAP) and mediolaterally (VML).

Each variable will be assessed in open or close eyes condition and firm or foam surface, respectively.

TheBBS will be used to measure dynamic balance. The BBS consists of 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.[98,99] This assesses the skills of sitting, standing, leaning, turning, and standing on a monopodal support. The BBS has proved to be reliable and valid for the study population.[91,92] The MCID for BBS has been set at 3 points for people with MS by Gervasonni et al.[100]

Fatigue

The MFIS is a self-reported questionnaire that evaluates the perceived impact of fatigue in patients with MS. This scale is composed of 21 items which assess the fatigue impact in three different domains. The global scale is divided into 9, 10, and 2 items that belong to the physical, cognitive, and psychosocial domains, respectively. The total score is 84, with higher scores indicating a higher impact of fatigue.[101,102] This scale is reliable and valid for measuring the impact of fatigue in subjects with MS.[103,104] MCID for MFIS has been established at 19.23% by Rietberg et al.[105] and 4 points by Scott et al.[106]

Quality of Life

To assess the changes perceived by participants in their quality of life, the reliable and valid multiple sclerosis quality of life scale 54 (MSQoL-54) will be used.[107] This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score ranges from 0 to 100. Higher values indicate a better quality of life.[108]

Data will be collected by a blinded physical therapist who is an expert in neurological and vestibular rehabilitation. The blind evaluation will be performed at several points in the study: before the intervention, at the end of the intervention, and at 3 and 6 months post-intervention (Table 4).

Sample size calculation

A major reason for conducting a pilot study is to determine the initial data to perform a sample size calculation for a larger trial.[77] For this reason, the formal sample size is not calculated. However, following the recommendations of good practice for the design and analysis of feasibility and pilot studies in preparation for RCT, [77, 78] we aimed to recruit at least 30 subjects (15 per group).

Statistical analysis

To assess the feasibility and safety of the experimental VRi intervention, a descriptive data analysis will be implemented, taking into consideration the pre-defined thresholds for the primary outcomes (Table 3). Participants' flow will be analysed to report the proportion of subjects who are eligible, consenting, adhering to intervention, and have retention rates at 3 and 6 months. These data will help to identify possible modifications in the definitive trial design.

The normal distribution of the variables will be assessed using the Shapiro-Wilk test. For normal distribution, data will be reported as mean ± standard deviation or as percentages. Similarly, for non-normal distribution, median, minimum and maximum values, and interquartile ranges (IQR) will be reported. Baseline differences between groups will be

analysed using the chi-square test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. This will help identify possible covariates.

Linear mixed models will be used to test group, time, and group-by-time interaction effects for all secondary variables. The analyses will be first unadjusted for any baseline characteristics and later adjusted for possible identified covariates (for example, gender or EDSS scores). An intention-to-treat approach will be used for data analysis.

Cohen´s criteria will be followed to assess the effect sizes of the studied variables, but due to the pilot nature of the study, all the effect analyses must be considered exploratory only. However, these data will help in sample size calculations in a definitive RCT. For all tests, $p < 0.05$ will be considered statistically significant. Graphical and numerical analysis of the data will be conducted using SPSS (version 25.0; IBM Corp, Armonk, NY, USA) and GraphPad PRISM (GraphPad Inc., San Diego, CA, USA).

Data management and monitoring

The research will not have an established data monitoring committee because the main decisions will be consensual between investigators. All data will be codified and recorded in an encrypted database by a number (in step of the subjects' name, for example) known only by the researcher team. The data will not be disclosed to third parties without participant consent.

Falls or any other adverse events derived during the intervention will be recorded by the therapists in a registry. These events will be communicated to the principal investigator of the study.

ETHICS AND DISSEMINATION

The study was approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). All participants will undergo and provide informed consent before data compilation. The investigators will disseminate the study results through literature in peer-reviewed scientific journals.

DISCUSSION

The current protocol for this pilot RCT aims to assess the feasibility and safety of vestibular rehabilitation in patients with MS through a VRi intervention compared with the conventional approach. Likewise, we will evaluate the changes that occurred in dizziness, postural control, fatigue, and quality of life for both study groups after the vestibular intervention.

Technical progress of VRi

Due to the intrinsic advantages of VRi and the multimodal design [109]of the protocol, the limitations of the Cawthorne-Cooksey training are expected to be overcome by

providing extrinsic feedback (game score and multisensorial stimulation) during exercise execution, cognitive and task-oriented training (exergames), and avoiding humdrum exercise repetitions because of the motivational and enjoyable environment . [50,109]

Owing to VRi tracking (gyroscopes, accelerometers, and magnetometers) and software systems that record head and corporal movements in six degrees of freedom, it is possible to perform exercises in different postural circumstances, similar to our experimental protocol (sitting down, standing, single leg support, tandem, and standing on foam surface), ensuring virtual environment verticality.[79,110] Furthermore, the command centre of movements and multisensory stimulation are primarily found at the cephalic level in HMD, making VRi a suitable device for vestibular rehabilitation.[86,111–113] Moreover, current VRi devices are affordable, own high-resolution graphics, higher frames per second, less delay and latency, and accurate software and hardware.[114,115] These enhance the sense of presence and immersion of the subject and reduce the possible appearance of cybersickness, as confirmed by Weech et al.[116]

Clinical applicability of VRi vestibular rehabilitation

The Cawthorne-Cooksey intervention, on which our VRi protocol is based, has been demonstrated to be effective in several populations, such as elderly people,[109] people with vertebrobasilar insufficiency,[117] and those with benign paroxysmal positional vertigo.[118] Thus, it is expected that the vestibular VRi intervention based on this gold standard could be effective in the mentioned populations, in addition to MS. However, to confirm this statement, extensive research is needed. In contrast, previous studies have reported the effectiveness of VRi in vestibular rehabilitation for unilateral vestibular hypofunction,[44,46] Ménière disease,[41,42] and traumatic brain injury.[119] On the other hand, the recent systematic review by Soltani et al.[120] supports HMD as a feasible and safe intervention to improve balance in older adults; because of this, we expect that VRi vestibular intervention will be safe and feasible in MS population [66,121–123].

Finally, telerehabilitation strategies combined with VR have been poorly studied in the MS population.[124] A recent study with ten MS participants showed satisfactory results in balance and gait, but not for fatigue, after a telerehabilitation intervention based on Nintendo Wii exergames.[125] With regard to our protocol, because Oculus Quest is wireless and portable, exercises can be performed at the laboratory, in public, in private clinics, and at home. In addition, this HMD has two features to ensure safety. The first is a restricted game zone to avoid blows, and on getting out, the real physical context will be displayed on the headset. Second, the virtual content of the session can be supervised through the Oculus app or via streaming, which is essential in telerehabilitation or home-based programs.[126]

Declaration of conflicting interests.

Authors of this papers declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

CGM, MDCV and MJCH conceptualised and designed the study. CGM wrote the first draft of the manuscript with critical input from MJCH. MDCV, MJCH, JCHR, EPP and RPC contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

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Table 1. Description of initial phase of vestibular intervention in both groups of study base on convectional protocol of Cawthorne- Cooksey exercises

Block of exercises	CG: Duration/ repetitions	CG intervention: Cawthorne- Cooksey protocol	EG intervention: adaptation of Cawthorne-Cooksey protocol to **virtual environments**	EG: Duration/ repetition
Sit down: eyes and head movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Stare a finger put in front of the face; move it closer and farther	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	24 minutes (combination of two blocks is performed because some exercises are answered by the same exergame) - Main room of First Steps: 11 minutes (10 slow repetitions and then 10 faster repetitions) - Shots in the Space: 7 minutes (all guns) - Beat saber:3 minutes (1 song) - Dance with
		2. Move the head to the right and the left, with open eyes	**First Steps: Main room and Shots in the Space**. Move and object in front of eyes and follow it + Shooting targets that appeared in the exergame	
		3. Move the head up and down, with open eyes	**Shots in the Space (First Steps).** Shooting target that appeared randomly inside the virtual environment	
		4. Look up and down while the head is fixed	**Beat Saber + Main room of First Step.** Cutting blocks with saber while head is fixed / hit a ball in the main room and fixated gaze on its movement while head is fixed	
		5. Look to the right and left while the head is fixed		
		6. Repeat exercise 4 and 5 in close eyes condition	Not possible in virtual environment	
Sit down: head and body movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Look an object placed in the floor. Then bring it above the head and place it again on the floor. Along all the movement look to the object.	**Main room of First Steps** Take a block from the virtual desk and bring to the floor and then above your head, while staring at it	
		2. Shrink your shoulders and do circular movements	**Dance with Robot (First Steps)** Shrink shoulder while dancing with a Robot	
		3. Bend forward and move an object around your knees	**Main room of First Steps** Bend forward and move a virtual block between the knees	

				Robot: 3 minutes
Standing up exercises	15 minutes Each exercise will be performed 5 slow repetitions and then 5 faster repetitions	1. Sit down and stand up and vice versa with open eyes	**Beat saber**	21 minutes - Beat sabe: 3 minutes (1 song) - Baseball: 8 minutes - Tennis: 4 minutes - Bowling: 6 minutes
		2. Sit down and stand up and vice versa with close eyes	Not possible in virtual environment	
		3. Stand up moving to the right while standing	**Bowling (Sports Scrambles)** Stand up moving to the right or the left while taking a bowling ball	
		4. Stand up moving to the left while standing		
		5. In front of your face, throw a ball from one hand to the other	**Baseball/ Tennis (Sports Scrambles)** Throw or hit a ball in front of your face	
		6. Under the knee level, throw a ball from one hand to the other	**Bowling (Sports Scrambles)** Throw the ball to hit the bowls under the knee level	

Table 2. Description of advanced phase of vestibular exercises for both groups

Exercises for both groups	CG: Duration and frequency	Control group	Experimental group	EG: Duration and frequency
1. Changing from sitting to standing and vice versa	10 repetitions	From a situation of sitting in a chair stand up and throw a ball	**Main room of First Steps** Take a block from virtual desk and when the subject stands up throw it a virtual sign situated inside the virtual environment	10 repetitions
2. Move and throw an object from one hand to the other while standing with feet together. Staring all the time to the object.	10 repetitions moving the object 10 repetitions throwing the object	Move a ball at eyes level and then throw it from one hand to the other	**Main room of First Steps** Move a virtual block at eyes level Take a virtual block and throw it from one hand to the other	10 repetitions moving the object 10 repetitions throwing the object
3. 360º turn	10 repetitions to the right/left	Turn 360º degrees and throw a ball to a target	**Main room of First Steps** Take a virtual block, turn 360 º and throw it to a located target in the environment	10 repetitions to the right/left
4. Moving the head with narrow base of support	15 repetitions (Example: 1 repetition look to the right)	Move head to right and left with feet together	**Main room of First Steps** In standing position with narrow base of support hit a ball and follow with the head its movements	5 repetitions (Example: 1 repetition is until the ball stops)
5. Stare an object put in front of the face; move it closer and farther while standing on foam surface	10 slow repetitions 10 fast repetitions	Stare a small ball and move it closer or farther to your face	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	10 slow repetitions 10 fast repetitions
6. Fast side head movements while standing on foam surface	15 repetitions	Throwing a ball to the right and left to the left while standing on a foam surface. Follow the ball with the head	**Main room of First Steps** Take the pin-pong racquet and hit blocks to one side and another following them with the head	15 repetitions

7. Move and object to the floor and bring it above your head while standing on a foam surface	10 repetitions	Taking a ball and make the exercise	**Main room of First Steps** Taking a virtual block from the desk perform the exercise	10 repetitions
8. Head movements while alternative single leg support	15 repetitions	Look to the right and the left while you maintain a monopodal balance	**Shots in the Space (First Steps)** Shooting targets just with one pistol, while single leg support	1 game
9. Head movements in a tandem position	15 repetitions	Look to one side and other while maintaining a tandem position	**Shots in the Space** Shooting targets with double gun while you maintain a tandem position	1 game
10. Head movements while standing on a foam surface	15 repetitions	Look to one side and other while standing on a foam surface	**Shots in the Space** Shooting targets with a machine gun while standing on a foam surface	1 game
11. Ocular movements with fixed head while standing on foam surface	20 repetitions (5 to right/left, 5 up/5 down)	Move eyes with fixed head while standing on a foam surface	**Beat Saber** Hit and cut blocks in a specific direction with sabers while standing on a foam surface	1 game
12. Throw a ball while standing on a foam surface	15 repetitions	Throw a ball to the physiotherapist and catch it again	**Baseball (Sports Scrambles)** Throw the ball in a baseball stadium while standing on a foam surface	1 game
13. Bowling with narrow base of support	10 repetitions	Bowl with feet together	**Bowling (Sports Scrambles)** Bowl with feet together	1 game
14. Bowling while standing on a foam surface	10 repetitions	Perform the exercise	**Bowling (Sports Scrambles)** Perform the exercise	1 game
15. Head movements while walking through a corridor	20 repetitions	Walk down a corridor while moving head	**Bowling (Sports Scrambles)** Walk down a bowling alley, while moving head side to side and the throw the bowling ball	2 games

Table 3. Primary outcomes pre-defined thresholds.

Feasibility measurements	**Measure**	**Pre-defined thresholds**
Recruitment/participation rate [85]	Proportion of potential participants who agree to complete screening and consent to participate	≥65%
Adherence rate [86]	Proportion of participants who attend and complete the intervention	≥80%
Retention rate [85]	Proportion of participants with complete study data at 3 and 6 months follow-up	≥75%
Usability [87,88]	SUS	≥60 points
Safety measurements		
Cybersickness [89]	SSQ	≤ 15 points
Fatigue to exercise [90]	ROF	≤ 4 points
Adverse events	Session's registry	No between groups differences

ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

Table 4. Data collection

Data and outcomes of study	Assessment details	Screening and recruitment	Baseline T0	During intervention	After intervention T1	Follow-up at 3 months T2	Follow-up at 6 months T3
Eligibility assessment		X					
Demographic variables		X					
Feasibility	Recruitment rate Adherence rate Retention rate Usability: SUS Individual semi-structured interview				X		
Safety	Cybersickness: SSQ Fatigue to exercise: ROF Falls/ adverse events registry			X			
Dizziness	DHI		X		X	X	X
Static Balance	Biodex Balance System: Length, antero-posterior, mediolateral sway, and velocity of centre of pressure. Open and close eyes condition. Firm or foam surface.		X		X	X	X
Dynamic Balance	BBS		X		X	X	X
Fatigue	MFIS		X		X	X	X
Quality of life	MSQoL-54		X		X	X	X

DHI: Dizziness Handicap inventory; BBS: Berg Balance Scale; MFIS: Modified Fatigue Impact Scale; MSQoL-54: Multiple Sclerosis Quality of Life- 54; ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

FIGURES LENGEND

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc. 1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

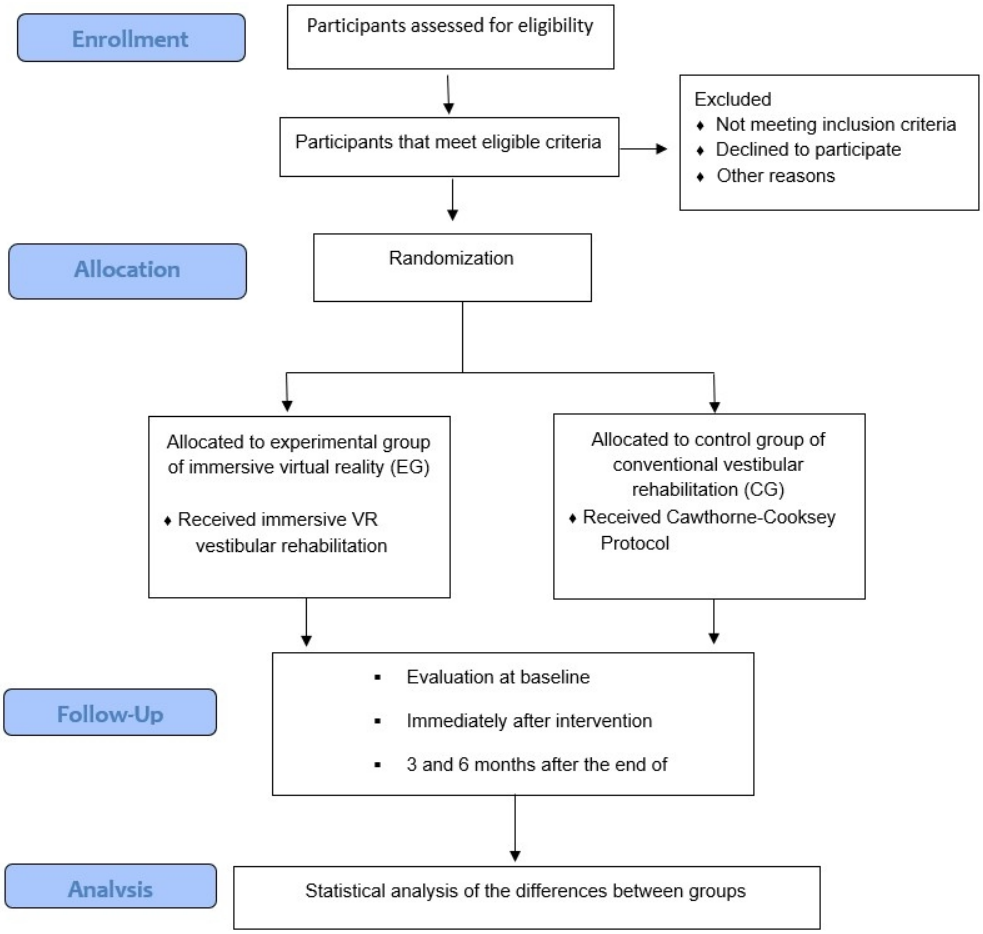

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

169x157mm (120 x 120 DPI)

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219x154mm (120 x 120 DPI)

Model Informed Consent Form

Study Title*:* **Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial**

Principal investigator: Cristina García Muñoz

Organization: University of Seville

This informed consent is formed by two parts:

I. **Information sheet**
II. **Certificate of Consent**

A copy of this form will be provided to you, in order you can take as much time as you need to make the final decision.

Part I: Information sheet

A. Introduction

This informed consent form is for people with multiple sclerosis who suffer from dizziness, vertigo or imbalance. We are inviting you to participate in the research driven by our research team at the Physical therapy Department of the University of Seville (Spain). The current research was reviewed and approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). This study complies with the Helsinki Statement. The aim of this form is to provide you with enough information to help you in your participation decision. Please, before you decide, read the information below carefully and feel free to ask the investigator if you have any question. The information will help you to understand the objective of study, procedures and duration and the possible benefits or risk derived from the research.

B. Background

Dizziness, balance disorders and fatigue are common clinical manifestation in multiple sclerosis (MS) having a direct impact in quality of life. Dizziness could affect between of 49-59 % of MS patients, and it is highly related to imbalance. This problem could have a peripheral or central vestibular origin in this population. Thus, MS population could be benefit from a vestibular rehabilitation program. Major goals of vestibular rehabilitation are to decrease symptoms of dizziness, improve ocular fixation, improve stability and its effects on daily living activities. Immersive virtual reality (VRi) is a booming tool in vestibular and neurorehabilitation because of its added advantages. However, VRi has obtained promising results reducing dizziness and improving balance in patients with peripheral vestibular disorders, no previous studies can be found in MS. That is why it is necessary to examine the feasibility and safety of the VRi as a vestibular rehabilitation intervention to improve dizziness, balance, fatigue, and quality of life in people with multiple sclerosis. Both groups of study will receive the same intervention with the only difference of the performance of the exercises trough the VRi device. This study purposes a VRi intervention based on the gold standard vestibular protocol Cawthorne-Cooksey. Improvements of symptoms will have a direct repercussion in the quality of life of MS

patients. To examine these effects, up to 30 participants may join the experimental intervention purpose in this research applying a seven week intervention period.

C. Purpose of study

To assess feasibility and safety of the experimental VRi vestibular protocol.

To examine the changes in dizziness, balance, fatigue and quality of life after a VRi vestibular protocol compared to conventional vestibular rehabilitation.

Procedure

Your participation in this research is completely voluntary. Experimental intervention will not have any cost to you. If you decide to reject your participation, once you have singed the informed consent form, you are entirely free to do it. You only must notify your desire to the principal investigator. You will not be required to give reasons for your decision to leave the research process. No ethics or economics conflicts will be carried out because of your rejection to participate. If you are willing to participate, before you enrolled the study you need to sing this informed consent form. Before you start with therapy you will participate in a baseline assessment drive by a physical therapist trained in vestibular rehabilitation. This initial evaluation will take place at Physiotherapy Department of the University of Seville. This initial assessment is constituted by:

- Dizziness Handicap Inventory (DHI): is a self-assessment questionnaire of 25 items. The aim of DHI is to evaluate the impact of dizziness on the quality of life. Higher scores of the questionnaire means more impact of dizziness in quality of life.
- Static balance will be evaluated by the Biodex Balance System. The mentioned balance system allows registration of the location of the centre of pressure.
- The Berg Balance Scale (BBS) is the selected instrument to measure dynamic balance. BBS is constituted by 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.
- Modified Fatigue Impact Scale (MFIS): self-reported questionnaire that evaluates the perceived impact of fatigue in MS patients. This scale is composed of 21-items which assess fatigue impact in three different domains.
- Multiple Sclerosis Quality of Life Scale 54 (MSQoL-54): This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score range is from 0 to 100 scales. Higher values indicate better quality of life

Once the baseline assessment ends, vestibular rehabilitation will be administered by a qualified physical therapist.

During sessions, physical therapist will be near to you to avoid possible falls. If any falls or another adverse event occurs during session it will be register by the therapist. To assess the possible appearance of Cybersicknes (nausea, dizziness, vomitus due to the VRi) Simulator Sickness Questionnaire will be provided to you by the therapist.

- Simulator Sickness Questionnaire (SSQ): The SSQ consists of a 16-item questionnaire divided into 3 categories: nausea, oculomotor and disorientation. Scores ranging between 10 and 15 mean significant symptoms, and above 20 indicates a simulator problem.

- Rating-of-Fatigue Scale (ROF): It is employed to quantify fatigue during the performance of exercise. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted).

Once the intervention ends you will return to the University of Seville for a post-intervention revaluation in which same test and questionnaires will be provided to you. Only System Usability Scale will be new in the evaluation process.

- System Usability Scale (SUS): SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means strongly disagree and 5 means strongly agree. The overall score can range from 0 to 100.

Also, a semi-structured interview will be carried out individually after the end of intervention to know main perception and impression experienced by participants during the experimental training.

A reassessment 3 and 6 month after the end of the intervention will be carried out at the University.

D. Study design

This study is a randomised control clinical trial in which is compared two different interventions each one in a defined group. The participants' allocation will be randomised into experimental group and control group. Evaluators will be blinded to intervention and group assignation; this is known as single-blind. Both groups will receive a total of 20 session based on gold standard protocol of Cawthorne-Cooksey. Is necessary to compare an immersive virtual reality intervention (VRi) to Cawthorne-Cooksey to know the real effects and possible benefits associated to virtual reality. Specialist vestibular physical therapist will monitor and supervise sessions.

- Control group intervention: Gradual exposition to vestibular exercises will be provided by 10 initial session and 10 advanced. Each session will last 50 minutes with 5 minutes of rest at the middle of the session. Session will be performed 3 times per week along 7 weeks. Vestibular exercises will be the same in both groups based on the conventional Cawthorne-Cooksey vestibular training.
- Experimental group: Same frequency and duration of intervention will be carried out in the experimental group. Also, vestibular exercises based on Cawthome-Cooksey will be the same in both groups. The main difference in the experimental groups consist of the performance of exercises through the Oculus Quest system. Oculus Quest is a head mounted display through you can interact with a virtual reality environment. Exercises will be adapted to be execute in the virtual environment provided by exergames called: *First Steps, Beat Saber* and *Sport Scrambles*. Exergames can be defined as the videogame which allows to reproduce immediately external actions of the subject to the virtual world.

.

E. Duration

The study starts at baseline assessment followed by administration of 20 session along 7 weeks. Once the intervention ends: DHI, Biodex Balance System, BBS, MFIS, MSQoL-54 VDAL, and SUS will be assessed and filled once more to examine the possible changes of outcomes. Reassessment will be made 3 and 6 months after the end of intervention. We will ask you to meet you at the University, 4 times in total owe to the evaluation process. Your participation in the research take place over 9 months in total.

F. Benefits

After the experimental intervention dizziness, balance, fatigue, and quality of life may improve or be resolved.

Risks

The participation on this study may involve the following risk:

- Possible apparition of pain in extremities derived from the physical exercise
- Slight possibility of transient nausea or dizziness
- Appearance of cybersickness during the performance of exercises through Oculus Quest.
- Possible falls. To reduce this possibility your participation will be supervised by the physical therapist.

G. Reminders and responsibilities

- Notify the research team if you wish to leave the study
- Follow the instructions given by investigators to achieve homogeneous course of the intervention
- Ask investigators if you any doubt or you do not understand something
- Tell investigators if you experience health changes during the research

H. Confidentiality

The information collect from the study will be kept confidential. Considering to data protection law you can modified or deny the access to them getting in touch to the principal investigator. Your personal data (name, age, address…) will be registered in a database in the Spanish Data Protection Agency. All your data will be codified by a number (in step of your name for example) known only by researchers. The research team is the only one authorized to manage your personal data through a confidential password. Your data will not be disclosed to third parties without your consent.

I. Sharing the results

Results from the study will be share in Scientifics conference or meetings. Furthermore, the study results will be disseminated via publication in peer-reviewed scientific journals. Private or confidential information will not be published or shared.

J. Conflict of interest

Authors of this paper declared no potential conflicts of interest respect to the research. The research team only is interested in completing this study. The investigators interest should not affect your consideration for participating.

K. Right to Refuse or Withdraw

This is a reconfirmation that you are completely free to accept or decline the offer to participate in this study. Also, you are entirely free to leave the research at any point without giving reasons.

L. Questions about the study

If you have any questions or doubts about the research (before, during or after the study) or you would like to speak to the research team, please contact to the main investigator: physical therapist Cristina García (+34) 954 55 14 71.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand that I am entirely free to leave the study at any moment after informing the principal investigator. I promised to follow the team research indications as much as possible. I know the possible benefits or risk derived from the experimental intervention. A signed and dated copy of the informed consent form will be given to me. I agree voluntarily to participate as a participant in the research titled: Feasibility of an immersive virtual reality-based vestibular rehabilitation program for dizziness, balance, and fatigue improvement in people with multiple sclerosis: pilot randomised controlled study

Patient signature: _____ Date: _____

I have provided a detailed information of the study to the participant including the possible benefits and risks. I have witnessed the accurate reading of the consent form to the potential participant. I have answered all doubts of the participant related to the research. I confirm that the individual has given consent freely.

Investigator signature: _____ Date: _____

Decline participation

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand

that I am entirely free to leave the study at any moment after informing the principal investigator. Although, I refuse to participate in the research proposed in this informed consent form.

Patient signature: _____ Date: _____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____2_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a_____
Protocol version	3	Date and version identifier	_____n/a_____
Funding	4	Sources and types of financial, material, and other support	_____13_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,13_____
	5b	Name and contact information for the trial sponsor	____n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____13_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____13_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4,5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8 + Table 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_Table 3,10____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_Table 3, 8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___5_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___6_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___6_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___8,10_____ __
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__8_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8,11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,11
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Keywords: multiple sclerosis; dizziness; postural balance; fatigue; virtual reality.

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

ABSTRACT

Introduction

Vestibular system damage in patients with Multiple Sclerosis (MS) may have a central and/or peripheral origin. Subsequent vestibular impairments may contribute to dizziness, balance disorders, and fatigue; common symptoms in patients with MS. Vestibular rehabilitation targeting vestibular impairments may improve these symptoms. Furthermore, as shown a successful tool in neurological rehabilitation, immersive virtual reality (VR) may augment vestibular rehabilitation interventions.

Methods and analysis

This protocol describes a parallel-arm, pilot randomised controlled trial (RCT), with blinded assessments, in 30 patients with MS with vestibular impairment (Dizziness Handicap Inventory ≥ 16). The experimental group will receive an immersive virtual reality (VRi) vestibular rehabilitation intervention based on the conventional Cawthorne-Cooksey protocol; the control group will perform the conventional protocol. The duration of the intervention in both groups is seven weeks (20 sessions, 3 sessions/week). The primary outcomes are the feasibility and safety of the vestibular VRi intervention in patients with MS. Secondary outcome measures are dizziness symptoms, balance performance, fatigue, and quality of life. Quantitative assessment will be carried out at baseline, immediately after intervention, and after a follow-up period of 3 and 6 months. Additionally, to complement quantitative data a qualitative assessment was performed after the intervention to examine feasibility and to future perspectives.

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee, Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). Informed consent will be collected from participants who wish to participate in the research. The results of this research will be disseminated by publication in peer-reviewed scientific journals.

Trial registration number ClinicalTrials.gov NCT04497025.

Keywords: multiple sclerosis, vestibular diseases, dizziness, postural balance, fatigue, physical therapy modalities, virtual reality.

ARTICLE SUMMARY

Strengths and limitations of the study

- As the VRi intervention (experimental group) is developed and based on the Cawthorne-Cooksey conventional vestibular rehabilitation protocol (control group), it allows a homogeneous comparison between study groups.

- The VRi systems offer multisensory feedback, oriented tasks, and repetitions of exercises in a ludic environment, thereby overcoming some of the limitations of the Cawthorne-Cooksey vestibular protocol.
- Blinding of participants and therapists is not possible due to the type of intervention.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation, demyelination of the central nervous system, and axonal loss.[1,2] Balance disorders, dizziness, and fatigue are among the most common and troublesome symptoms in MS, repercussing on quality of life.[2–7] Fatigue has been reported the most disabling in MS, of which impairments in central sensory integration may be an underlying cause [8,9]. Furthermore, fatigue can be enhanced by vestibular symptoms such as vertigo, dizziness, and imbalance. [10,11]

There are a myriad of vestibular system disorders, which could have a peripheral (inner ear, vestibular nerve), central (brainstem and cerebellar), origin or both.[12–14] Balance problems, lack of coordination in cephalic movement with regard to the body, ocular disturbances, and dizziness are symptoms related to vestibular disorders, as well as MS. [11,15–17] Postural deficits are associated with problems of the subjective visual vertical and dizziness during head movements, which are mediated by the vestibulo-ocular reflex (VOR).[15,18–20] Furthermore, impairments in the vestibulo-spinal reflex (VSR) can cause postural problems due to an inappropriate muscle response in imbalance situations.[20–24]. Central demyelination and/or peripheral disturbances can be possible aetiologies of vestibular impairments and their clinical manifestation in MS.[25–28] Furthermore, the presence of vestibular impairment and their clinical manifestation may be affected by disease progression.[14,25–27] Specifically, patients with brainstem involvement, as identified using the Expanded Disability Status Scale (EDSS) could be showing signs of imbalance, vestibular disorders, and greater disability.[29,30]

Vestibular rehabilitation consists of exercises that provide accurate spatial information of the head with regard to body position whilst stimulating VOR, VSR, and somatosensory information.[4,31–34] Based on mechanisms of substitution, adaptation, and habituation,[6,33] vestibular rehabilitation can be effective in addressing peripheral and central vestibular impairments.[26,35,36] Patients with MS therefore benefit from goals of vestibular rehabilitation, being decrease dizziness, improve ocular fixation and stability, and performance in daily living activities.[33,37–39]

Conventional vestibular rehabilitation consists of repetitive exercises and movements driven to improve physical or psychological impairments due to vestibular problems. [40] Nowadays, Cawthorne- Cooksey vestibular training is considered the protocol of reference withing this framework.[31,41] Although further research is needed, conventional vestibular training has been reported as superior to no intervention and at least as effective than exercise-based approach (Frenkel exercises and endurance training) for improving dizziness, balance, and fatigue in any MS type. [38,39] Currently, there is

an exponential growth of studies that evaluate the effectiveness of virtual reality (VR) applied to vestibular rehabilitation in other diseases.[42–50] The effectiveness of non-immersive VR for balance and gait training in patients with MS has been already proven.[51] Moreover, a systematic review found that immersive virtual reality (VRi) presents additional clinical benefits when compared to conventional vestibular training (performance and repetition of exercises in a motivational environment, oriented tasks, multisensory stimulation, extrinsic feedback, and promotion of adherence).[52–57] The VR induces neuroplastic changes in neurological affection as MS.[58] Within VRi, the modality that integrates physical activity in a virtual environment with mentioned advantages is exergame, that has proven to be effective for neurological diseases.[59,60] Moreover, despite exercising through a VR system, it is perceived as less exhausting [61], whilst the subject is expose to a large variety of environments boosting the vestibular mechanism of habituation. [37,62] VRi allows the subject to complete immersion within the 360º virtual environment, enhancing the feeling of presence.[63–65] To the best of our knowledge, no previous research on VRi and vestibular rehabilitation in MS has been performed.

Therefore, the primary purpose of this study is to determine the feasibility and safety of a VRi-based vestibular rehabilitation program in MS population. Second, we aim to preliminarily evaluate the preliminarily effects of the vestibular VRi exercise protocol in comparison with conventional vestibular training for improvement in dizziness, balance, fatigue, and quality of life in patients with MS.

METHODS AND ANALYSIS

Study design

This protocol describes a two-arm, parallel group, pilot randomised clinical trial (RCT), with blinded assessment. An initial evaluation of the study sample is, followed by an intervention period of 7 weeks for both the experimental and control group. A further three assessments will then be carried out immediately after intervention and after follow-up periods of 3 and 6 months. The study design is illustrated in Figure 1.

This protocol meets the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[66] This RCT will also be developed following instructions from the Consolidated Standards of Reporting Trials (CONSORT).[67] It has been registered at ClinicalTrials.gov with the identifier NCT04497025.

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Sevilla (Spain). The Virgen Macarena Hospital will be the main healthcare institution involved in this study. The inclusion of other healthcare centres in the area is expected.

Participants and recruitment

Recruitment of participants is expected to start in September 2021 and end in September 2022. All subjects that potentially meet the eligibility criteria will be contacted to

participate in the study. Those who decide to participate and meet the eligibility criteria will be asked for written informed consent (please see supplemental material for informed consent form).

Inclusion Criteria:

• Both male and female subjects aged 18-65 years

• Clinically diagnosed with any type of MS in accordance with the revised McDonald criteria. This will be assessed based on clinical history by a medical team.

• Walking ability according to the Expanded Disability Status Scale score (EDSS ≤ 6). This will be assessed based on clinical history by a medical team.

• Brainstem or cerebellar involvement with ≥ 2 points in the second functional system of the EDSS.[68] This will be evaluated based on clinical history by a medical team.

• Objective presence of dizziness symptoms (Dizziness Handicap Inventory (DHI) ≥ 16). This will be assessed after informed consent acceptance by an expert vestibular physical therapist.

• Presence of fatigue (Modified Fatigue Impact Scale (MFIS) ≥ 38)[69] or balance problems (Berg Balance Scale (BBS) ≤ 47).[70]. This will be evaluated after the acceptance of participation in the study by an expert vestibular physical therapist.

Exclusion Criteria:

• Partial or complete blindness

• Cognitive impairment (Mini-Mental State Examination score ≤ 24)

• Another neurologic disorder contributing to balance impairment

• Disease relapse within the last 3 months (transitory exacerbations of the disease by the appearance of neurological clinical manifestations imbalance, dizziness, and more)[27,71,72]

• Changes in MS pharmacotherapy within the last 3 months

• History of vestibular rehabilitation within the last 6 months

• Acute cardiovascular or respiratory illnesses

• Contraindications to VRi use (epilepsy, spatiotemporal disorientation, and cognitive impairment)

• Any other contraindications to physical activity

Exclusion criteria will be assessed based on clinical history by a medical team.

Randomisation, concealment allocation, and blinding

Participants will be randomly allocated to one of the two intervention groups by an independent researcher, using 1:1 distribution ratio and a computer-generated random sequence. The independent researcher will oversee the randomisation process and place the allocation of participants in sealed and concealed envelopes. This researcher will inform participants of their random allocation and will provide them the informed consent forms. An expert physical therapist in vestibular rehabilitation will perform the intervention. The assessor will remain blinded to the participants' groups allocation.

Patient and public involvement

No patients or public were involved in designing the trial, but a number of public organisations have been contacted for patient recruitment (for example, Hospital Virgen Macarena, Ilustre Colegio Profesional de Fisioterapeutas de Andalucía). However, study participants will play a significant role in remodelling the intervention and tailor it to the specific need of patients with MS bases on their experiences in the present study. As such, a qualitative evaluation of the experimental VRi vestibular training, performed through the semi-structured interview process for each participant, has been included. Once the study is completed, participants will be informed about it by e-mail in a comprehensible writing style. Through the triangulation qualitative method, a presentation of results to the participants will provide an unique angle to the interpretation of study finding [73]. Furthermore, the researchers will host meetings in each public organisation engaged in recruitment.

Interventions

Conventional Vestibular Rehabilitation Protocol (CG)

The control group (CG) will perform the conventional vestibular rehabilitation Cawthorne-Cooksey protocol exercises.[31] These exercises aim to restore balance affected by vestibular dysfunction and train the vestibular system. Subsequently, this may improves vestibular compensation through a mechanism of neuroplasticity, known as adaptation, habituation, and substitution.[37,62,74] The primary goal of these mechanisms is to adapt the VOR and VSR, habituate and substitute head movements that provoke vestibular and balance symptoms, and train dynamic balance.

As shown in Table 1, exercises are divided into three blocks, which will be performed slowly at first and then progressively faster. Participants allocated to the CG will receive this conventional protocol three times per week for 7 weeks. Each session will last for 50 min, and the rest time will be for at least 5 min. A total of 10 initial sessions and 10 advanced sessions will be carried out. Based on previous studies, during the initial phase, exercises of the first and second blocks will be carried out by 10 slow repetitions and 10 fast repetitions.[75,76] The third block exercises will be repeated five times slowly and then five times more quickly. The complete intervention time for each block is 15 min (Table 1). Once participants have exceeded the first ten sessions, they will begin with more complex exercises. To developed these advanced vestibular exercises for both groups, the principles and keys of Cawthorne-Cooksey,[31] Han et al.[37] and Whitney

et al.[62] were assumed. The advanced phases of the intervention for participants in the control group are described in Table 2. This intervention matches the experimental group (EG), with the only difference being that exercises are not performed in an immersive virtual environment. The exercise parameters in the advanced sessions described in order of difficulty within the session are the amplitude of the support base, alternative single leg support, tandem position, unstable surface, and walking while head movements. To avoid the appearance of vestibular symptoms during exercises, the parameters to progress exercises will be carried out in the specific order mentioned above. These parameters provide proprioceptive disturbances and encourage vestibular training through substitution of neural mechanisms. [37,62] Other parameters that train habituation and adaptation mechanisms include the increasing speed of head movement or its range of motion.[37,62] All parameters can be adapted to patient characteristics and progress with each session (for example, modifying the base of support from higher to lower amplitude on the firm and unstable surface).

The vestibular program will be conducted by an experienced vestibular rehabilitation physical therapist, who will provide verbal indications and stay near the participants to lend them confidence and decrease the risk of falling during the session.

Immersive Virtual Reality Intervention (EG)

Participants assigned to the EG will receive VRi vestibular rehabilitation through the head-mounted display (HMD) Oculus Quest (Facebook technologies). VRi allows complete immersion in a 360º virtual environment and enables interaction. Virtual immersive rehabilitation can only be achieved with the use of a VR headset or HMD. In this protocol, the new generation Oculus Quest equipment has been selected, which has some added advantages compared to other similar HMDs. These advantages include the absence of movement sensors or laptop installations, wireless option, portability, and a reduced risk of suffering from cybersickness syndrome, owing to the high resolution and accurate movement capture.[77,78]

To achieve homogeneous interventions between the two groups, the VRi intervention have been designed based on the gold standard Cawthorne-Cooksey vestibular protocol. Subjects in this group will receive the same number of sessions and duration as the CG. Similar to the CG, the first 10 sessions of the VRi treatment will be carried out in the sitting down position (eyes and head movement/head and body movement) and the last one as standing up exercises. The number of repetitions and adaptation of VRi equated to the conventional protocol for immersive virtual environments during the initial phase are described in Table 1. In the initial phase, the advance phase exercises will be the same in both groups, with the main difference being the interaction with the immersive virtual environment. The advance phases of vestibular rehabilitation and the VRi-adapted exercises are shown in Table 2. The exercise parameters described in the CG will be applied in the EG as well. In addition, to prevent falls over interaction with virtual environments, participants will be monitored and supervised by an expert physical therapist.

First Steps, Beat Saber demo and Sport Scrambles demo games will be displayed using the Oculus Quest HMD to apply the vestibular protocol. These games reflect a first-person exergame environment in which subject actions are recreated virtually.

Furthermore, all selected games are commercially available and have free access in the Oculus app to anyone who owns an HMD device. *First Steps* is the onset game of Oculus, in which one learns to use the VRi device in a playable way. This game consists of the *Main room* where the subject can interact with virtual objects as virtual blocks, pin-pong racket and ball, hanging ball, and more. First Steps also contains two additional virtual environments. The first is a shooter game called *Shots in the Space*, which aims to reach the highest score while shooting random targets at a space station. This shooter offers three options: a single gun, a double gun, or a machine gun, which will be included in exercises. The second is *Dance with Robot*, in which one dances and interacts with a robot. *Beat saber* is a rhythm music game in which blocks are slashed in a specific direction with a red (left hand) and blue (right hand) saber, while trying to avoid some obstacles. *Sport Scrambles* consist of three sports games: baseball, tennis, and bowling, in which one must defeat their opponent while balls, rackets, or your baseball bat are randomly changing into a giraffe, a cheese, and so on. The virtual scenarios are shown in Figure 2.

Outcomes and measurements

The primary outcomes will include the feasibility and safety of the experimental VRi vestibular protocol. The feasibility of the study will be assessed using recruitment, adherence, retention rates, and usability of the VRi device. In addition to quantitative assessment, qualitative data semi-structured interviews will be conducted with those participating in the VRi intervention. The interview will be carried out by the therapist in charge of the intervention. This qualitative strategy allows to obtain a deeper understanding of the participants' experiences of the VRi intervention received. Safety will be examined by the appearance of cybersickness and fatigue to exercise along the virtual reality treatment and a registry of falls and other adverse events. Pre-defined thresholds for considering the feasibility and safety of the VRi intervention are described in Table 3. [79–84]

Secondary outcomes include changes in dizziness, balance, fatigue, and quality of life after a VRi vestibular protocol compared with conventional vestibular rehabilitation.

Usability of the Virtual Reality System

In combination with participation, retention, and adherence to treatment rates, feasibility will be evaluated using the System Usability Scale (SUS). The SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means 'strongly disagree' and 5 means 'strongly agree'. The overall score ranges from 0 to 100, which is obtained by multiplying the sum of every item by 2.5. A higher score indicates higher usability.[81,82] To maintain the blindness of the assessor, this measurement will be performed by the physiotherapist who conducted the intervention.

Cybersickness Syndrome

To assess the safety of the intervention along with the fall and adverse events registry, the appearance of cybersickness will be evaluated using the Simulator Sickness Questionnaire (SSQ). The SSQ is implemented to measure the appearance of sickness due to a virtual environment. The SSQ consists of a 16-item questionnaire divided into three categories: nausea, oculomotor, and disorientation.[85,86] Scores ranging between 10 and 15 indicate significant symptoms, and those above 20 indicate a simulator problem.[83] This scale will be provided by the physical therapist during each session.

Rating-of-Fatigue Scale

To examine safety along with the performance of the sessions, the appearance of fatigue related to exercise will be evaluated through Rating-of-Fatigue (ROF) [84]. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted). The main aim of this scale is to assess fatigue in myriad contexts while exercising or during daily living activities. The ROF will be presented to the participants in each session.

Dizziness

Dizziness symptoms will be assessed using the DHI. This self-assessment questionnaire consists of 25-items divided into the following subscales: physical, emotional, and functional. The physical and emotional subscales range from 0 to 36 points, and the functional subscale ranges from 0 to 28 points. The total score is 100, which relates to the highest level of disability and handicap.[87–89] This instrument is reliable and valid for the study population.[90,91] The minimal clinical importance difference (MCID) has been established at 18 points in patients with vestibular disorders.[89]

Balance

Static balance will be evaluated using the Biodex balance system. The aforementioned system allows the registration of the location of the centre of pressure (CoP).[92–94] Biodex has been proven to be a valid instrument for evaluating stability and postural control in subjects sith MS. [95,96] Moreover, Biodex can compute the following variables in relation to the CoP:

- Length (mm), the CoP trajectory throughout the platform surface.
- Anteroposterior (SAP) and mediolateral sway (SMS); these measure CoP deviation along each axis (mm).
- Velocity (mm/s) of CoP oscillation through the anteroposterior axis (VAP) and mediolaterally (VML).

Each variable will be assessed in open or close eyes condition and firm or foam surface, respectively.

TheBBS will be used to measure dynamic balance. The BBS consists of 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.[97,98] This assesses the skills of sitting, standing, leaning,

turning, and standing on a monopodal support. The BBS has proved to be reliable and valid for the study population.[90,91] The MCID for BBS has been set at 3 points for people with MS by Gervasonni et al.[99]

Fatigue

The MFIS is a self-reported questionnaire that evaluates the perceived impact of fatigue in patients with MS. This scale is composed of 21 items which assess the fatigue impact in three different domains. The global scale is divided into 9, 10, and 2 items that belong to the physical, cognitive, and psychosocial domains, respectively. The total score is 84, with higher scores indicating a higher impact of fatigue.[100,101] This scale is reliable and valid for measuring the impact of fatigue in patients with MS.[102,103] The MCID for MFIS has been established at 19.23% by Rietberg et al.[104] and 4 points by Scott et al.[105]

Quality of Life

To assess the changes perceived by participants in their quality of life, the reliable and valid multiple sclerosis quality of life scale 54 (MSQoL-54) will be used.[106] This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score ranges from 0 to 100. Higher values indicate a better quality of life.[107]

Data will be collected by a blinded physical therapist who is an expert in neurological and vestibular rehabilitation. The blind evaluation will be performed at several points in the study: before the intervention, at the end of the intervention, and at 3 and 6 months post-intervention (Table 4).

Sample size calculation

A major reason for conducting a pilot study is to determine the initial data to perform a sample size calculation for a larger trial.[77] For this reason, the formal sample size is not calculated. However, following the recommendations of good practice for the design and analysis of feasibility and pilot studies in preparation for RCT, [77, 78] we aimed to recruit at least 30 subjects (15 per group).

Statistical analysis

To assess the feasibility and safety of the experimental VRi intervention, a descriptive data analysis will be implemented, taking into consideration the pre-defined thresholds for the primary outcomes (Table 3). Participants' flow will be analysed to report the proportion of subjects who are eligible, consenting, adhering to intervention, and have retention rates at 3 and 6 months. These data will help to identify possible modifications in the definitive trial design when VRi is found feasible and safe.

The normal distribution of the variables will be assessed using the Shapiro-Wilk test. For normal distribution, data will be reported as mean ± standard deviation or as percentages. Similarly, for non-normal distribution, median, minimum, and maximum values, and interquartile ranges (IQR) will be reported. Baseline differences between groups will be analysed using the chi-square test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. This will help identify possible covariates.

Linear mixed models will be used to test group, time, and group-by-time interaction effects for all secondary variables on an intention-to-treat basis. The analyses will be first unadjusted for any baseline characteristics and later adjusted for possible identified covariates (for example, gender or EDSS scores).

Cohen´s criteria will be followed to value the effect sizes of the studied variables, though due to the pilot nature of the study, all the effect analyses must be considered exploratory only. Nonetheless, these data will help in sample size calculations for a definitive RCT. For all tests, $p < 0.05$ will be considered statistically significant. Graphical and numerical analysis of the data will be conducted using SPSS (version 25.0; IBM Corp, Armonk, NY, USA) and GraphPad PRISM (GraphPad Inc., San Diego, CA, USA).

Data management and monitoring

The study will not have an independent data monitoring committee because the main decisions will be agreed between the members of the research team. All data will be codified and recorded in an encrypted database by a number (instead of the subjects' name, for example) known only by the researcher team. The data will not be disclosed to third parties without participant consent.

Falls or any other adverse events derived during the intervention will be recorded by the therapists in a registry. These events will be communicated to the principal investigator of the study.

ETHICS AND DISSEMINATION

The study was approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). All participants will undergo and provide informed consent before data compilation. The investigators will disseminate the study results through literature in peer-reviewed scientific journals.

DISCUSSION

The current protocol for this pilot RCT aims to assess the feasibility and safety of vestibular rehabilitation in patients with MS through a VRi intervention compared with the conventional approach. Likewise, we will evaluate the changes that occurred in dizziness, postural control, fatigue, and quality of life for both study groups after the vestibular intervention.

Technical progress of VRi

The Cawthorne- Cooksey vestibular protocol presents some limitations like absence of exercise' feedback, no changes in support base or surface of work, lack of cognitive and task-oriented training so vestibular training is based on repetitive exercises perform without functional objective and variability in the performance environment [41,44]. Due to the intrinsic advantages of VRi and the multimodal design [108] of the protocol, the limitations of the Cawthorne-Cooksey training are expected to be overcome by providing extrinsic feedback (game score and multisensorial stimulation) during exercise execution, possibility of adding changes in surface and base of support during the performance, cognitive and task-oriented training (exergames), and avoiding humdrum exercise repetitions because of the motivational and enjoyable environment . [52,108]

Owing to VRi tracking (gyroscopes, accelerometers, and magnetometers) and software systems that record head and corporal movements in six degrees of freedom, it is possible to perform exercises in different postural circumstances, similar to our experimental protocol (sitting down, standing, single leg support, tandem, and standing on foam surface), ensuring virtual environment verticality.[78,109] Furthermore, the command centre of movements and multisensory stimulation are primarily found at the cephalic level in HMD, making VRi a suitable device for vestibular rehabilitation.[85,110–112] Moreover, current VRi devices are affordable, own high-resolution graphics, higher frames per second, less delay and latency, and accurate software and hardware.[113,114] These enhance the sense of presence and immersion of the subject and reduce the possible appearance of cybersickness, as confirmed by Weech et al.[115]

Clinical applicability of VRi vestibular rehabilitation

The Cawthorne-Cooksey intervention, on which our VRi protocol is based, has been demonstrated to be effective in several populations, such as elderly people,[108] people with vertebrobasilar insufficiency,[116] and those with benign paroxysmal positional vertigo.[117] Thus, arguably, vestibular VRi intervention based on this gold standard could be effective in the mentioned populations, including patients with MS. Prominsing previous studies have reported the effectiveness of VRi in vestibular rehabilitation for unilateral vestibular hypofunction,[46,48] Ménière disease,[43,44] and traumatic brain injury.[118] Moreover, a recent systematic review by Soltani et al.[119] supports HMD as a feasible and safe intervention to improve balance in older adults; because of this, we hypothesize that VRi vestibular intervention will be safe and feasible in MS population [120–123].

Finally, telerehabilitation strategies combined with VR have been poorly studied in the MS population.[124] A recent study with ten MS participants showed satisfactory results in balance and gait, but not for fatigue, after a telerehabilitation intervention based on Nintendo Wii exergames.[125] With regard to our protocol, because Oculus Quest is wireless and portable, exercises can be performed at the laboratory, in public, in private clinics, and at home. In addition, this HMD has two features to ensure safety. The first is a restricted game zone to avoid blows, and on getting out, the real physical context will be displayed on the headset. Second, the virtual content of the session can be supervised

through the Oculus app or via streaming, which is essential in telerehabilitation or home-based programs.[126]

Declaration of conflicting interests.

Authors of this papers declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

CGM, MDCV and MJCH conceptualised and designed the study. CGM wrote the first draft of the manuscript with critical input from MJCH. MDCV, MJCH, JCHR, EPP and RPC contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

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Table 1. Description of initial phase of vestibular intervention in both groups of study base on convectional protocol of Cawthorne- Cooksey exercises

Block of exercises	CG: Duration/ repetitions	CG intervention: Cawthorne- Cooksey protocol	EG intervention: adaptation of Cawthorne-Cooksey protocol to **virtual environments**	EG: Duration/ repetition
Sit down: eyes and head movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Stare a finger put in front of the face; move it closer and farther	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	24 minutes (combination of two blocks is performed because some exercises are answered by the same exergame) - Main room of First Steps: 11 minutes (10 slow repetitions and then 10 faster repetitions) - Shots in the Space: 7 minutes (all guns) - Beat saber:3 minutes (1 song) - Dance with
		2. Move the head to the right and the left, with open eyes	**First Steps: Main room and Shots in the Space**. Move and object in front of eyes and follow it + Shooting targets that appeared in the exergame	
		3. Move the head up and down, with open eyes	**Shots in the Space (First Steps).** Shooting target that appeared randomly inside the virtual environment	
		4. Look up and down while the head is fixed	**Beat Saber + Main room of First Step.** Cutting blocks with saber while head is fixed / hit a ball in the main room and fixated gaze on its movement while head is fixed	
		5. Look to the right and left while the head is fixed		
		6. Repeat exercise 4 and 5 in close eyes condition	Not possible in virtual environment	
Sit down: head and body movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Look an object placed in the floor. Then bring it above the head and place it again on the floor. Along all the movement look to the object.	**Main room of First Steps** Take a block from the virtual desk and bring to the floor and then above your head, while staring at it	
		2. Shrink your shoulders and do circular movements	**Dance with Robot (First Steps)** Shrink shoulder while dancing with a Robot	
		3. Bend forward and move an object around your knees	**Main room of First Steps** Bend forward and move a virtual block between the knees	

				Robot: 3 minutes
Standing up exercises	15 minutes Each exercise will be performed 5 slow repetitions and then 5 faster repetitions	1. Sit down and stand up and vice versa with open eyes	**Beat saber**	21 minutes - Beat sabe: 3 minutes (1 song) - Baseball: 8 minutes - Tennis: 4 minutes - Bowling: 6 minutes
		2. Sit down and stand up and vice versa with close eyes	Not possible in virtual environment	
		3. Stand up moving to the right while standing	**Bowling (Sports Scrambles)** Stand up moving to the right or the left while taking a bowling ball	
		4. Stand up moving to the left while standing		
		5. In front of your face, throw a ball from one hand to the other	**Baseball/ Tennis (Sports Scrambles)** Throw or hit a ball in front of your face	
		6. Under the knee level, throw a ball from one hand to the other	**Bowling (Sports Scrambles)** Throw the ball to hit the bowls under the knee level	

Table 2. Description of advanced phase of vestibular exercises for both groups

Exercises for both groups	CG: Duration and frequency	Control group	Experimental group	EG: Duration and frequency
1. Changing from sitting to standing and vice versa	10 repetitions	From a situation of sitting in a chair stand up and throw a ball	**Main room of First Steps** Take a block from virtual desk and when the subject stands up throw it a virtual sign situated inside the virtual environment	10 repetitions
2. Move and throw an object from one hand to the other while standing with feet together. Staring all the time to the object.	10 repetitions moving the object 10 repetitions throwing the object	Move a ball at eyes level and then throw it from one hand to the other	**Main room of First Steps** Move a virtual block at eyes level Take a virtual block and throw it from one hand to the other	10 repetitions moving the object 10 repetitions throwing the object
3. 360º turn	10 repetitions to the right/left	Turn 360º degrees and throw a ball to a target	**Main room of First Steps** Take a virtual block, turn 360 º and throw it to a located target in the environment	10 repetitions to the right/left
4. Moving the head with narrow base of support	15 repetitions (Example: 1 repetition look to the right)	Move head to right and left with feet together	**Main room of First Steps** In standing position with narrow base of support hit a ball and follow with the head its movements	5 repetitions (Example: 1 repetition is until the ball stops)
5. Stare an object put in front of the face; move it closer and farther while standing on foam surface	10 slow repetitions 10 fast repetitions	Stare a small ball and move it closer or farther to your face	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	10 slow repetitions 10 fast repetitions
6. Fast side head movements while standing on foam surface	15 repetitions	Throwing a ball to the right and left to the left while standing on a foam surface. Follow the ball with the head	**Main room of First Steps** Take the pin-pong racquet and hit blocks to one side and another following them with the head	15 repetitions

7. Move and object to the floor and bring it above your head while standing on a foam surface	10 repetitions	Taking a ball and make the exercise	**Main room of First Steps** Taking a virtual block from the desk perform the exercise	10 repetitions
8. Head movements while alternative single leg support	15 repetitions	Look to the right and the left while you maintain a monopodal balance	**Shots in the Space (First Steps)** Shooting targets just with one pistol, while single leg support	1 game
9. Head movements in a tandem position	15 repetitions	Look to one side and other while maintaining a tandem position	**Shots in the Space** Shooting targets with double gun while you maintain a tandem position	1 game
10. Head movements while standing on a foam surface	15 repetitions	Look to one side and other while standing on a foam surface	**Shots in the Space** Shooting targets with a machine gun while standing on a foam surface	1 game
11. Ocular movements with fixed head while standing on foam surface	20 repetitions (5 to right/left, 5 up/5 down)	Move eyes with fixed head while standing on a foam surface	**Beat Saber** Hit and cut blocks in a specific direction with sabers while standing on a foam surface	1 game
12. Throw a ball while standing on a foam surface	15 repetitions	Throw a ball to the physiotherapist and catch it again	**Baseball (Sports Scrambles)** Throw the ball in a baseball stadium while standing on a foam surface	1 game
13. Bowling with narrow base of support	10 repetitions	Bowl with feet together	**Bowling (Sports Scrambles)** Bowl with feet together	1 game
14. Bowling while standing on a foam surface	10 repetitions	Perform the exercise	**Bowling (Sports Scrambles)** Perform the exercise	1 game
15. Head movements while walking through a corridor	20 repetitions	Walk down a corridor while moving head	**Bowling (Sports Scrambles)** Walk down a bowling alley, while moving head side to side and the throw the bowling ball	2 games

Table 3. Primary outcomes pre-defined thresholds.

Feasibility measurements	**Measure**	**Pre-defined thresholds**
Recruitment/participation rate [85]	Proportion of potential participants who agree to complete screening and consent to participate	≥65%
Adherence rate [86]	Proportion of participants who attend and complete the intervention	≥80%
Retention rate [85]	Proportion of participants with complete study data at 3 and 6 months follow-up	≥75%
Usability [87,88]	SUS	≥60 points
Safety measurements		
Cybersickness [89]	SSQ	≤ 15 points
Fatigue to exercise [90]	ROF	≤ 4 points
Adverse events	Session's registry	No between groups differences

ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

Table 4. Data collection

Data and outcomes of study	Assessment details	Screening and recruitment	Baseline T0	During intervention	After intervention T1	Follow-up at 3 months T2	Follow-up at 6 months T3
Eligibility assessment		X					
Demographic variables		X					
Feasibility	Recruitment rate Adherence rate Retention rate Usability: SUS Individual semi-structured interview				X		
Safety	Cybersickness: SSQ Fatigue to exercise: ROF Falls/ adverse events registry			X			
Dizziness	DHI		X		X	X	X
Static Balance	Biodex Balance System: Length, antero-posterior, mediolateral sway, and velocity of centre of pressure. Open and close eyes condition. Firm or foam surface.		X		X	X	X
Dynamic Balance	BBS		X		X	X	X
Fatigue	MFIS		X		X	X	X
Quality of life	MSQoL-54		X		X	X	X

DHI: Dizziness Handicap inventory; BBS: Berg Balance Scale; MFIS: Modified Fatigue Impact Scale; MSQoL-54: Multiple Sclerosis Quality of Life- 54; ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

FIGURES LENGEND

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc. 1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

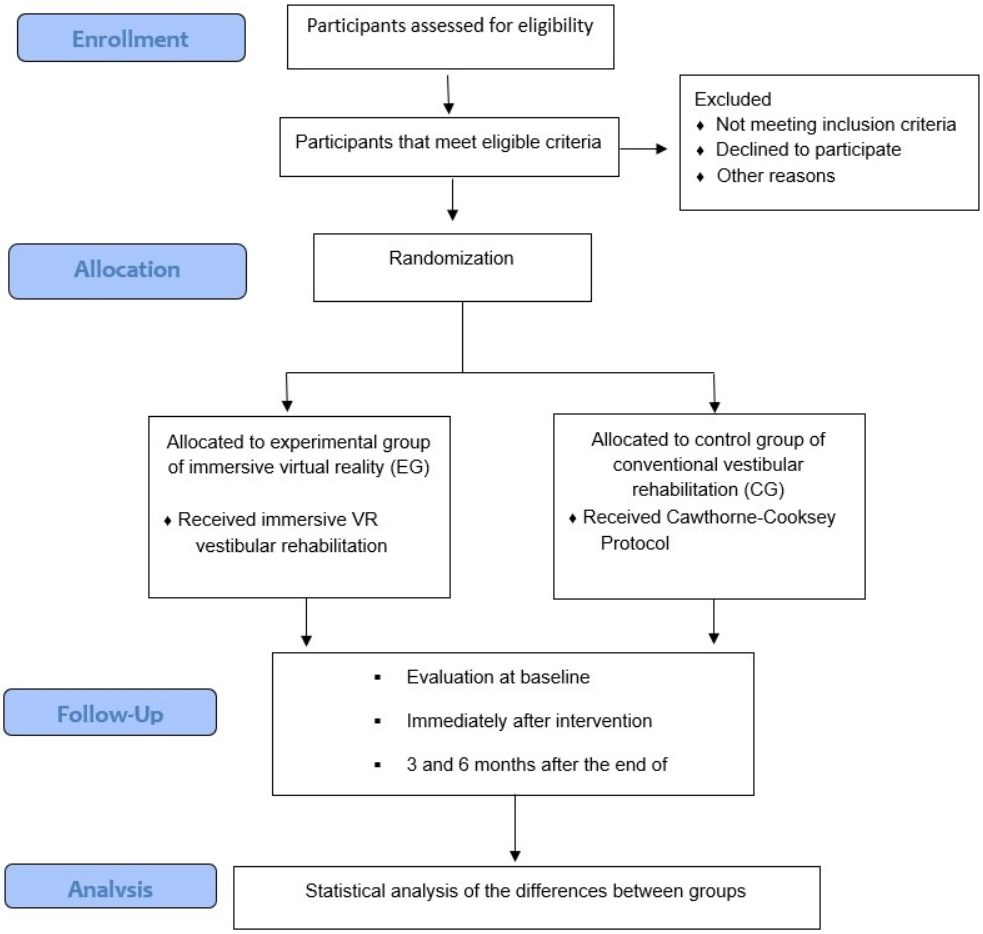

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

169x157mm (120 x 120 DPI)

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc. 1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

219x154mm (120 x 120 DPI)

Model Informed Consent Form

Study Title*:* **Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial**

Principal investigator: Cristina García Muñoz

Organization: University of Seville

This informed consent is formed by two parts:

I. **Information sheet**
II. **Certificate of Consent**

A copy of this form will be provided to you, in order you can take as much time as you need to make the final decision.

Part I: Information sheet

A. Introduction

This informed consent form is for people with multiple sclerosis who suffer from dizziness, vertigo or imbalance. We are inviting you to participate in the research driven by our research team at the Physical therapy Department of the University of Seville (Spain). The current research was reviewed and approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). This study complies with the Helsinki Statement. The aim of this form is to provide you with enough information to help you in your participation decision. Please, before you decide, read the information below carefully and feel free to ask the investigator if you have any question. The information will help you to understand the objective of study, procedures and duration and the possible benefits or risk derived from the research.

B. Background

Dizziness, balance disorders and fatigue are common clinical manifestation in multiple sclerosis (MS) having a direct impact in quality of life. Dizziness could affect between of 49-59 % of MS patients, and it is highly related to imbalance. This problem could have a peripheral or central vestibular origin in this population. Thus, MS population could be benefit from a vestibular rehabilitation program. Major goals of vestibular rehabilitation are to decrease symptoms of dizziness, improve ocular fixation, improve stability and its effects on daily living activities. Immersive virtual reality (VRi) is a booming tool in vestibular and neurorehabilitation because of its added advantages. However, VRi has obtained promising results reducing dizziness and improving balance in patients with peripheral vestibular disorders, no previous studies can be found in MS. That is why it is necessary to examine the feasibility and safety of the VRi as a vestibular rehabilitation intervention to improve dizziness, balance, fatigue, and quality of life in people with multiple sclerosis. Both groups of study will receive the same intervention with the only difference of the performance of the exercises trough the VRi device. This study purposes a VRi intervention based on the gold standard vestibular protocol Cawthorne-Cooksey. Improvements of symptoms will have a direct repercussion in the quality of life of MS

patients. To examine these effects, up to 30 participants may join the experimental intervention purpose in this research applying a seven week intervention period.

C. Purpose of study

To assess feasibility and safety of the experimental VRi vestibular protocol.

To examine the changes in dizziness, balance, fatigue and quality of life after a VRi vestibular protocol compared to conventional vestibular rehabilitation.

Procedure

Your participation in this research is completely voluntary. Experimental intervention will not have any cost to you. If you decide to reject your participation, once you have singed the informed consent form, you are entirely free to do it. You only must notify your desire to the principal investigator. You will not be required to give reasons for your decision to leave the research process. No ethics or economics conflicts will be carried out because of your rejection to participate. If you are willing to participate, before you enrolled the study you need to sing this informed consent form. Before you start with therapy you will participate in a baseline assessment drive by a physical therapist trained in vestibular rehabilitation. This initial evaluation will take place at Physiotherapy Department of the University of Seville. This initial assessment is constituted by:

- Dizziness Handicap Inventory (DHI): is a self-assessment questionnaire of 25 items. The aim of DHI is to evaluate the impact of dizziness on the quality of life. Higher scores of the questionnaire means more impact of dizziness in quality of life.
- Static balance will be evaluated by the Biodex Balance System. The mentioned balance system allows registration of the location of the centre of pressure.
- The Berg Balance Scale (BBS) is the selected instrument to measure dynamic balance. BBS is constituted by 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.
- Modified Fatigue Impact Scale (MFIS): self-reported questionnaire that evaluates the perceived impact of fatigue in MS patients. This scale is composed of 21-items which assess fatigue impact in three different domains.
- Multiple Sclerosis Quality of Life Scale 54 (MSQoL-54): This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score range is from 0 to 100 scales. Higher values indicate better quality of life

Once the baseline assessment ends, vestibular rehabilitation will be administered by a qualified physical therapist.

During sessions, physical therapist will be near to you to avoid possible falls. If any falls or another adverse event occurs during session it will be register by the therapist. To assess the possible appearance of Cybersicknes (nausea, dizziness, vomitus due to the VRi) Simulator Sickness Questionnaire will be provided to you by the therapist.

- Simulator Sickness Questionnaire (SSQ): The SSQ consists of a 16-item questionnaire divided into 3 categories: nausea, oculomotor and disorientation. Scores ranging between 10 and 15 mean significant symptoms, and above 20 indicates a simulator problem.

- Rating-of-Fatigue Scale (ROF): It is employed to quantify fatigue during the performance of exercise. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted).

Once the intervention ends you will return to the University of Seville for a post-intervention revaluation in which same test and questionnaires will be provided to you. Only System Usability Scale will be new in the evaluation process.

- System Usability Scale (SUS): SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means strongly disagree and 5 means strongly agree. The overall score can range from 0 to 100.

Also, a semi-structured interview will be carried out individually after the end of intervention to know main perception and impression experienced by participants during the experimental training.

A reassessment 3 and 6 month after the end of the intervention will be carried out at the University.

D. Study design

This study is a randomised control clinical trial in which is compared two different interventions each one in a defined group. The participants' allocation will be randomised into experimental group and control group. Evaluators will be blinded to intervention and group assignation; this is known as single-blind. Both groups will receive a total of 20 session based on gold standard protocol of Cawthorne-Cooksey. Is necessary to compare an immersive virtual reality intervention (VRi) to Cawthorne-Cooksey to know the real effects and possible benefits associated to virtual reality. Specialist vestibular physical therapist will monitor and supervise sessions.

- Control group intervention: Gradual exposition to vestibular exercises will be provided by 10 initial session and 10 advanced. Each session will last 50 minutes with 5 minutes of rest at the middle of the session. Session will be performed 3 times per week along 7 weeks. Vestibular exercises will be the same in both groups based on the conventional Cawthorne-Cooksey vestibular training.
- Experimental group: Same frequency and duration of intervention will be carried out in the experimental group. Also, vestibular exercises based on Cawthome-Cooksey will be the same in both groups. The main difference in the experimental groups consist of the performance of exercises through the Oculus Quest system. Oculus Quest is a head mounted display through you can interact with a virtual reality environment. Exercises will be adapted to be execute in the virtual environment provided by exergames called: *First Steps, Beat Saber* and *Sport Scrambles*. Exergames can be defined as the videogame which allows to reproduce immediately external actions of the subject to the virtual world.

.

E. Duration

The study starts at baseline assessment followed by administration of 20 session along 7 weeks. Once the intervention ends: DHI, Biodex Balance System, BBS, MFIS, MSQoL-54 VDAL, and SUS will be assessed and filled once more to examine the possible changes of outcomes. Reassessment will be made 3 and 6 months after the end of intervention. We will ask you to meet you at the University, 4 times in total owe to the evaluation process. Your participation in the research take place over 9 months in total.

F. Benefits

After the experimental intervention dizziness, balance, fatigue, and quality of life may improve or be resolved.

Risks

The participation on this study may involve the following risk:

- Possible apparition of pain in extremities derived from the physical exercise
- Slight possibility of transient nausea or dizziness
- Appearance of cybersickness during the performance of exercises through Oculus Quest.
- Possible falls. To reduce this possibility your participation will be supervised by the physical therapist.

G. Reminders and responsibilities

- Notify the research team if you wish to leave the study
- Follow the instructions given by investigators to achieve homogeneous course of the intervention
- Ask investigators if you any doubt or you do not understand something
- Tell investigators if you experience health changes during the research

H. Confidentiality

The information collect from the study will be kept confidential. Considering to data protection law you can modified or deny the access to them getting in touch to the principal investigator. Your personal data (name, age, address…) will be registered in a database in the Spanish Data Protection Agency. All your data will be codified by a number (in step of your name for example) known only by researchers. The research team is the only one authorized to manage your personal data through a confidential password. Your data will not be disclosed to third parties without your consent.

I. Sharing the results

Results from the study will be share in Scientifics conference or meetings. Furthermore, the study results will be disseminated via publication in peer-reviewed scientific journals. Private or confidential information will not be published or shared.

J. Conflict of interest

Authors of this paper declared no potential conflicts of interest respect to the research. The research team only is interested in completing this study. The investigators interest should not affect your consideration for participating.

K. Right to Refuse or Withdraw

This is a reconfirmation that you are completely free to accept or decline the offer to participate in this study. Also, you are entirely free to leave the research at any point without giving reasons.

L. Questions about the study

If you have any questions or doubts about the research (before, during or after the study) or you would like to speak to the research team, please contact to the main investigator: physical therapist Cristina García (+34) 954 55 14 71.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand that I am entirely free to leave the study at any moment after informing the principal investigator. I promised to follow the team research indications as much as possible. I know the possible benefits or risk derived from the experimental intervention. A signed and dated copy of the informed consent form will be given to me. I agree voluntarily to participate as a participant in the research titled: Feasibility of an immersive virtual reality-based vestibular rehabilitation program for dizziness, balance, and fatigue improvement in people with multiple sclerosis: pilot randomised controlled study

Patient signature: _____ Date: _____

I have provided a detailed information of the study to the participant including the possible benefits and risks. I have witnessed the accurate reading of the consent form to the potential participant. I have answered all doubts of the participant related to the research. I confirm that the individual has given consent freely.

Investigator signature: _____ Date: _____

Decline participation

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand

that I am entirely free to leave the study at any moment after informing the principal investigator. Although, I refuse to participate in the research proposed in this informed consent form.

Patient signature: _____ Date: _____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____2_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a_____
Protocol version	3	Date and version identifier	_____n/a_____
Funding	4	Sources and types of financial, material, and other support	_____13_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,13_____
	5b	Name and contact information for the trial sponsor	____n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____13_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____13_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4,5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8 + Table 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_Table 3,10____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_Table 3, 8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___5_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___6_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___6_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___8,10_____ __
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__8_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8,11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,11
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

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Keywords: multiple sclerosis; dizziness; postural balance; fatigue; virtual reality.

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Title:

Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial

ABSTRACT

Introduction

Vestibular system damage in patients with Multiple Sclerosis (MS) may have a central and/or peripheral origin. Subsequent vestibular impairments may contribute to dizziness, balance disorders, and fatigue in this population.. Vestibular rehabilitation targeting vestibular impairments may improve these symptoms. Furthermore, as a successful tool in neurological rehabilitation, immersive virtual reality (VR) could also be implemented within a vestibular rehabilitation intervention.

Methods and analysis

This protocol describes a parallel-arm, pilot randomised controlled trial (RCT), with blinded assessments, in 30 patients with MS with vestibular impairment (Dizziness Handicap Inventory ≥ 16). The experimental group will receive an immersive virtual reality (VRi) vestibular rehabilitation intervention based on the conventional Cawthorne-Cooksey protocol; the control group will perform the conventional protocol. The duration of the intervention in both groups will be seven weeks (20 sessions, 3 sessions/week). The primary outcomes are the feasibility and safety of the vestibular VRi intervention in patients with MS. Secondary outcome measures are dizziness symptoms, balance performance, fatigue, and quality of life. Quantitative assessment will be carried out at baseline (T0), immediately after intervention (T1), and after a follow-up period of 3 and 6 months (T2 and T3). Additionally, in order to further examine the feasibility of the intervention, a qualitative assessment will be performed at T1.

Ethics and dissemination

The study was approved by the Andalusian Review Board and Ethics Committee, Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). Informed consent will be collected from participants who wish to participate in the research. The results of this research will be disseminated by publication in peer-reviewed scientific journals.

Trial registration number ClinicalTrials.gov NCT04497025.

Keywords: multiple sclerosis, vestibular diseases, dizziness, postural balance, fatigue, physical therapy modalities, virtual reality.

ARTICLE SUMMARY

Strengths and limitations of the study

- As the VRi intervention (experimental group) is developed and based on the Cawthorne-Cooksey conventional vestibular rehabilitation protocol (control group), it allows a homogeneous comparison between study groups.
- The VRi systems offer multisensory feedback, oriented tasks, and repetitions of exercises in a ludic environment, thereby overcoming some of the limitations of the Cawthorne-Cooksey vestibular protocol.
- Blinding of participants and therapists is not possible due to the type of intervention.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation, demyelination of the central nervous system, and axonal loss.[1,2] Balance disorders, dizziness, and fatigue are among the most common and troublesome symptoms in MS, repercussing on quality of life.[2–7] Fatigue is the most disabling manifestation in MS, of which impairments in central sensory integration may be an underlying cause [8,9]. Furthermore, fatigue can be enhanced by vestibular symptoms such as vertigo, dizziness, and imbalance. [10,11]

There are a myriad of vestibular system disorders, which could have a peripheral (inner ear, vestibular nerve), central (brainstem and cerebellar), origin or both.[12–14] Balance problems, lack of coordination in cephalic movement with regard to the body, ocular disturbances, and dizziness are symptoms related to vestibular disorders, as well as MS. [11,15–17] Postural deficits are associated with problems of the subjective visual vertical and dizziness during head movements, which are mediated by the vestibulo-ocular reflex (VOR).[15,18–20] Furthermore, impairments in the vestibulo-spinal reflex (VSR) can cause postural problems due to an inappropriate muscle response in imbalance situations.[20–24]. Central demyelination and/or peripheral disturbances can be possible aetiologies of vestibular impairments and their clinical manifestation in MS.[25–28] Furthermore, the presence of vestibular impairments and their clinical manifestations may be affected by the progression of the disease.[14,25–27] Specifically, patients with brainstem involvement, as identified using the Expanded Disability Status Scale (EDSS) could be showing signs of imbalance, vestibular disorders, and greater disability.[29,30]

Vestibular rehabilitation consists of exercises that provide accurate spatial information of the head with regard to body position whilst stimulating VOR, VSR, and somatosensory information.[4,31–34] Based on mechanisms of substitution, adaptation, and habituation,[6,33] vestibular rehabilitation can be effective in addressing peripheral and central vestibular impairments.[26,35,36] Patients with MS therefore benefit from goals of vestibular rehabilitation, being decrease dizziness, improve ocular fixation and stability, and performance in daily living activities.[33,37–39]

Conventional vestibular rehabilitation consists of repetitive exercises and movements driven to improve physical or psychological impairments due to vestibular problems. [40] Nowadays, Cawthorne- Cooksey vestibular training is considered the gold standard protocol within this framework.[31,41] Although further research is needed, conventional

vestibular training has been reported as superior to no intervention and at least as effective than exercise-based approach (Frenkel exercises and endurance training) for improving dizziness, balance, and fatigue in any MS type. [38,39] Currently, there is an exponential growth of studies that evaluate the effectiveness of virtual reality (VR) applied to vestibular rehabilitation in other diseases.[42–50] The effectiveness of non-immersive VR for balance and gait training in patients with MS has been already proven.[51] Moreover, a systematic review found that immersive virtual reality (VRi) presents additional clinical benefits when compared to conventional vestibular training (performance and repetition of exercises in a motivational environment, oriented tasks, multisensory stimulation, extrinsic feedback, and promotion of adherence).[52–57] The VR induces neuroplastic changes in neurological affection as MS.[58] Within VRi, the modality that integrates physical activity in a virtual environment with mentioned advantages is exergame, that has proven to be effective for neurological diseases.[59,60] Moreover, despite exercising through a VR system, it is perceived as less exhausting [61], whilst the subject is expose to a large variety of environments boosting the vestibular mechanism of habituation. [37,62] VRi allows the subject to complete immersion within the 360º virtual environment, enhancing the feeling of presence.[63–65] To the best of our knowledge, no previous research on VRi and vestibular rehabilitation in MS has been performed.

Therefore, the primary purpose of this study is to determine the feasibility and safety of a VRi-based vestibular rehabilitation program in MS population. Second, we aim to preliminarily evaluate the preliminarily effects of the vestibular VRi exercise protocol in comparison with conventional vestibular training for improvement in dizziness, balance, fatigue, and quality of life in patients with MS.

METHODS AND ANALYSIS

Study design

This protocol describes a two-arm, parallel group, pilot randomised clinical trial (RCT), with blinded assessment. An initial evaluation of the study sample (T0) will be followed by an intervention period of 7 weeks for both the experimental and control group. A further three assessments will then be carried out immediately after intervention (T1) and after follow-up periods of 3 (T2) and 6 months (T3). The study design is illustrated in Figure 1.

This protocol meets the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[66] This RCT will also be developed following instructions from the Consolidated Standards of Reporting Trials (CONSORT).[67] It has been registered at ClinicalTrials.gov with the identifier NCT04497025.

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Sevilla (Spain). The Virgen Macarena Hospital will be the main healthcare institution involved in this study. The inclusion of other healthcare centres in the area is expected.

Participants and recruitment

Recruitment of participants is expected to start in September 2021 and end in September 2022. All subjects that potentially meet the eligibility criteria will be contacted to participate in the study. Those who decide to participate and meet the eligibility criteria will be asked for written informed consent (please see supplemental material for informed consent form).

Inclusion Criteria:

• Both male and female subjects aged 18-65 years

• Clinically diagnosed with any type of MS in accordance with the revised McDonald criteria. This will be assessed based on clinical history by a medical team.

• Walking ability according to the Expanded Disability Status Scale score (EDSS ≤ 6). This will be assessed based on clinical history by a medical team.

• Brainstem or cerebellar involvement with ≥ 2 points in the second functional system of the EDSS.[68] This will be evaluated based on clinical history by a medical team.

• Objective presence of dizziness symptoms (Dizziness Handicap Inventory (DHI) ≥ 16). This will be assessed after informed consent acceptance by an expert vestibular physical therapist.

• Presence of fatigue (Modified Fatigue Impact Scale (MFIS) ≥ 38)[69] or balance problems (Berg Balance Scale (BBS) ≤ 47).[70]. This will be evaluated after the acceptance of participation in the study by an expert vestibular physical therapist.

Exclusion Criteria:

• Partial or complete blindness

• Cognitive impairment (Mini-Mental State Examination score ≤ 24)

• Another neurologic disorder contributing to balance impairment

• Disease relapse within the last 3 months (transitory exacerbations of the disease by the appearance of neurological clinical manifestations imbalance, dizziness, and more)[27,71,72]

• Changes in MS pharmacotherapy within the last 3 months

• History of vestibular rehabilitation within the last 6 months

• Acute cardiovascular or respiratory illnesses

• Contraindications to VRi use (epilepsy, spatiotemporal disorientation, and cognitive impairment)

• Any other contraindications to physical activity

Exclusion criteria will be assessed based on clinical history by a medical team.

Randomisation, concealment allocation, and blinding

Participants will be randomly allocated to one of the two intervention groups by an independent researcher, using 1:1 distribution ratio and a computer-generated random sequence. The independent researcher will oversee the randomisation process and place the allocation of participants in sealed and concealed envelopes. This researcher will inform participants of their random allocation and will provide them the informed consent forms. An expert physical therapist in vestibular rehabilitation will perform the intervention. The assessor will remain blinded to the participants' groups .

Patient and public involvement

No patients or public are involved in designing the trial, but a number of public organisations will be contacted for patient recruitment (for example, Hospital Virgen Macarena, Ilustre Colegio Profesional de Fisioterapeutas de Andalucía). However, based on their experiences in this pilot study, participants will play a significant role in remodelling the intervention and tailor it to the specific needs of patients with MS. For this purpose, a qualitative evaluation performed through a semi-structured interview process for each participant will be included. This triangulation method will help us to interpret the study findings [73].

Once the study is completed, participants will be informed about it by e-mail in a comprehensible writing style. Furthermore, the researchers will host meetings in each public organisation engaged in recruitment.

Interventions

Conventional Vestibular Rehabilitation Protocol (CG)

The control group (CG) will perform the conventional vestibular rehabilitation Cawthorne-Cooksey protocol exercises.[31] These exercises aim to restore balance affected by vestibular dysfunction and train the vestibular system. Subsequently, this may improves vestibular compensation through a mechanism of neuroplasticity, known as adaptation, habituation, and substitution.[37,62,74] The primary goal of these mechanisms is to adapt the VOR and VSR, habituate and substitute head movements that provoke vestibular and balance symptoms, and train dynamic balance.

As shown in Table 1, exercises are divided into three blocks, which will be performed slowly at first and then progressively faster. Participants allocated to the CG will receive this conventional protocol three times per week for 7 weeks. Each session will last for 50 min, and the rest time will be for at least 5 min. A total of 10 initial sessions and 10 advanced sessions will be carried out. Based on previous studies, during the initial phase, exercises of the first and second blocks will be carried out by 10 slow repetitions and 10 fast repetitions.[75,76] The third block exercises will be repeated five times slowly and then five times more quickly. The complete intervention time for each block is 15 min (Table 1). Once participants have exceeded the first ten sessions, they will begin with more complex exercises. To developed these advanced vestibular exercises for both

groups, the principles and keys of Cawthorne-Cooksey,[31] Han et al.[37] and Whitney et al.[62] were assumed. The advanced phases of the intervention for participants in the control group are described in Table 2. This intervention matches the experimental group (EG), with the only difference being that exercises are not performed in an immersive virtual environment. The exercise parameters in the advanced sessions are the amplitude of the support base, alternative single leg support, tandem position, unstable surface, and walking while head movements. To avoid the appearance of vestibular symptoms during exercises, these parameters will be carried out in the specific order mentioned above. These parameters provide proprioceptive disturbances and encourage vestibular training through substitution of neural mechanisms. [37,62] Other parameters that train habituation and adaptation mechanisms include the increasing speed of head movement or its range of motion.[37,62] All parameters can be adapted to patient characteristics and progress with each session (for example, modifying the base of support from higher to lower amplitude on the firm and unstable surface).

The vestibular program will be conducted by an experienced vestibular rehabilitation physical therapist, who will provide verbal indications and stay near the participants to lend them confidence and decrease the risk of falling during the session.

Immersive Virtual Reality Intervention (EG)

Participants assigned to the EG will receive VRi vestibular rehabilitation through the head-mounted display (HMD) Oculus Quest (Facebook technologies). VRi allows complete immersion in a 360º virtual environment and enables interaction. Virtual immersive rehabilitation can only be achieved with the use of a VR headset or HMD. In this protocol, the new generation Oculus Quest equipment has been selected, which has some added advantages compared to other similar HMDs. These advantages include the absence of movement sensors or laptop installations, wireless option, portability, and a reduced risk of suffering from cybersickness syndrome, owing to the high resolution and accurate movement capture.[77,78]

To achieve homogeneous interventions between the two groups, the VRi intervention has been designed based on the gold standard Cawthorne-Cooksey vestibular protocol. Subjects in this group will receive the same number of sessions and duration as the CG. Similar to the CG, the first 10 sessions of the VRi treatment will be carried out in the sitting down position (eyes and head movement/head and body movement) and the last one as standing up exercises. The number of repetitions and adaptation of VRi equated to the conventional protocol for immersive virtual environments during the initial phase are described in Table 1. In the initial phase, the advance phase exercises will be the same in both groups, with the main difference being the interaction with the immersive virtual environment. The advance phases of vestibular rehabilitation and the VRi-adapted exercises are shown in Table 2. The exercise parameters described in the CG will be applied in the EG as well. In addition, to prevent falls over interaction with virtual environments, participants will be monitored and supervised by an expert physical therapist.

First Steps, Beat Saber demo and Sport Scrambles demo games will be displayed using the Oculus Quest HMD to apply the vestibular protocol. These games reflect a first-person exergame environment in which subject actions are recreated virtually.

Furthermore, all selected games are commercially available and have free access in the Oculus app to anyone who owns an HMD device. *First Steps* is the onset game of Oculus, in which one learns to use the VRi device in a playable way. This game consists of the *Main room* where the subject can interact with virtual objects as virtual blocks, pin-pong racket and ball, hanging ball, and more. First Steps also contains two additional virtual environments. The first is a shooter game called *Shots in the Space*, which aims to reach the highest score while shooting random targets at a space station. This shooter offers three options: a single gun, a double gun, or a machine gun, which will be included in exercises. The second is *Dance with Robot*, in which one dances and interacts with a robot. *Beat saber* is a rhythm music game in which blocks are slashed in a specific direction with a red (left hand) and blue (right hand) saber, while trying to avoid some obstacles. *Sport Scrambles* consist of three sports games: baseball, tennis, and bowling, in which one must defeat their opponent while balls, rackets, or your baseball bat are randomly changing into a giraffe, a cheese, and so on. The virtual scenarios are shown in Figure 2.

Outcomes and measurements

The primary outcomes will include the feasibility and safety of the experimental VRi vestibular protocol. The feasibility of the study will be assessed using recruitment, adherence, retention rates, and usability of the VRi device. In addition to this quantitative assessment, semi-structured interviews will be conducted with the VRi intervention participants. The interview will be carried out by the therapist in charge of the intervention. This qualitative strategy is expected to allow a deeper understanding of the participants' experiences. Safety will be examined by the appearance of cybersickness and fatigue to exercise along the virtual reality treatment and a registry of falls and other adverse events. Pre-defined thresholds for considering the feasibility and safety of the VRi intervention are described in Table 3. [79–84]

Secondary outcomes include changes in dizziness, balance, fatigue, and quality of life after a VRi vestibular protocol compared with conventional vestibular rehabilitation.

Usability of the Virtual Reality System

In combination with participation, retention, and adherence to treatment rates, feasibility will be evaluated using the System Usability Scale (SUS). The SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means 'strongly disagree' and 5 means 'strongly agree'. The overall score ranges from 0 to 100, which is obtained by multiplying the sum of every item by 2.5. A higher score indicates higher usability.[81,82] To maintain the blindness of the assessor, this measurement will be performed by the physiotherapist who conducted the intervention.

Cybersickness Syndrome

To assess the safety of the intervention along with the fall and adverse events registry, the appearance of cybersickness will be evaluated using the Simulator Sickness Questionnaire (SSQ). The SSQ is implemented to measure the appearance of sickness due to a virtual environment. The SSQ consists of a 16-item questionnaire divided into three categories: nausea, oculomotor, and disorientation.[85,86] Scores ranging between 10 and 15 indicate significant symptoms, and those above 20 indicate a simulator problem.[83] This scale will be provided by the physical therapist during each session.

Rating-of-Fatigue Scale

To examine safety along with the performance of the sessions, the appearance of fatigue related to exercise will be evaluated through Rating-of-Fatigue (ROF) [84]. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted). The main aim of this scale is to assess fatigue in myriad contexts while exercising or during daily living activities. The ROF will be presented to the participants in each session.

Dizziness

Dizziness symptoms will be assessed using the DHI. This self-assessment questionnaire consists of 25-items divided into the following subscales: physical, emotional, and functional. The physical and emotional subscales range from 0 to 36 points, and the functional subscale ranges from 0 to 28 points. The total score is 100, which relates to the highest level of disability and handicap.[87–89] This instrument is reliable and valid for the study population.[90,91] The minimal clinical importance difference (MCID) has been established at 18 points in patients with vestibular disorders.[89]

Balance

Static balance will be evaluated using the Biodex balance system. The aforementioned system allows the registration of the location of the centre of pressure (CoP).[92–94] Biodex has been proven to be a valid instrument for evaluating stability and postural control in subjects sith MS. [95,96] Moreover, Biodex can compute the following variables in relation to the CoP:

- Length (mm), the CoP trajectory throughout the platform surface.
- Anteroposterior (SAP) and mediolateral sway (SMS); these measure CoP deviation along each axis (mm).
- Velocity (mm/s) of CoP oscillation through the anteroposterior axis (VAP) and mediolaterally (VML).

Each variable will be assessed in open or close eyes condition and firm or foam surface, respectively.

TheBBS will be used to measure dynamic balance. The BBS consists of 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.[97,98] This assesses the skills of sitting, standing, leaning, turning, and standing on a monopodal support. The BBS has proved to be reliable and valid for the study population.[90,91] The MCID for BBS has been set at 3 points for people with MS by Gervasonni et al.[99]

Fatigue

The MFIS is a self-reported questionnaire that evaluates the perceived impact of fatigue in patients with MS. This scale is composed of 21 items which assess the fatigue impact in three different domains. The global scale is divided into 9, 10, and 2 items that belong to the physical, cognitive, and psychosocial domains, respectively. The total score is 84, with higher scores indicating a higher impact of fatigue.[100,101] This scale is reliable and valid for measuring the impact of fatigue in patients with MS.[102,103] The MCID for MFIS has been established at 19.23% by Rietberg et al.[104] and 4 points by Scott et al.[105]

Quality of Life

To assess the changes perceived by participants in their quality of life, the reliable and valid multiple sclerosis quality of life scale 54 (MSQoL-54) will be used.[106] This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score ranges from 0 to 100. Higher values indicate a better quality of life.[107]

Data will be collected by a blinded physical therapist who is an expert in neurological and vestibular rehabilitation. The blind evaluation will be performed at several points in the study: before the intervention, at the end of the intervention, and at 3 and 6 months post-intervention (Table 4).

Sample size calculation

A major reason for conducting a pilot study is to determine the initial data to perform a sample size calculation for a larger trial.[77] For this reason, the formal sample size will not be carried out. However, following the recommendations of good practice for the design and analysis of feasibility and pilot studies in preparation for RCT, [77, 78] we aimed to recruit at least 30 subjects (15 per group).

Statistical analysis

To assess the feasibility and safety of the experimental VRi intervention, a descriptive data analysis will be implemented, taking into consideration the pre-defined thresholds for the primary outcomes (Table 3). Participants' flow will be analysed to report the proportion of subjects who are eligible, consenting, adhering to intervention, and have

retention rates at 3 and 6 months. These data will help to identify possible modifications in the definitive trial design when VRi is found feasible and safe.

The normal distribution of the variables will be assessed using the Shapiro-Wilk test. For normal distribution, data will be reported as mean ± standard deviation or as percentages. Similarly, for non-normal distribution, median, minimum, and maximum values, and interquartile ranges (IQR) will be reported. Baseline differences between groups will be analysed using the chi-square test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. This will help identify possible covariates.

Linear mixed models will be used to test group, time, and group-by-time interaction effects for all secondary variables on an intention-to-treat basis. The analyses will be first unadjusted for any baseline characteristics and later adjusted for possible identified covariates (for example, gender or EDSS scores).

Cohen´s criteria will be followed to value the effect sizes of the studied variables, though due to the pilot nature of the study, all the effect analyses must be considered exploratory only. Nonetheless, these data will help in sample size calculations for a definitive RCT. For all tests, $p < 0.05$ will be considered statistically significant. Graphical and numerical analysis of the data will be conducted using SPSS (version 25.0; IBM Corp, Armonk, NY, USA) and GraphPad PRISM (GraphPad Inc., San Diego, CA, USA).

Data management and monitoring

The study will not have an independent data monitoring committee because the main decisions will be agreed between the members of the research team. All data will be codified and recorded in an encrypted database by a number (instead of the subjects' name, for example) known only by the researcher team. The data will not be disclosed to third parties without participant consent.

Falls or any other adverse events derived during the intervention will be recorded by the therapists in a registry. These events will be communicated to the principal investigator of the study.

ETHICS AND DISSEMINATION

The study was approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). All participants will undergo and provide informed consent before data compilation. The investigators will disseminate the study results through literature in peer-reviewed scientific journals.

DISCUSSION

The current protocol for this pilot RCT aims to assess the feasibility and safety of vestibular rehabilitation in patients with MS through a VRi intervention compared with the conventional approach. Likewise, we will evaluate the changes that occurred in

dizziness, postural control, fatigue, and quality of life for both study groups after the vestibular intervention.

Technical progress of VRi

The Cawthorne- Cooksey vestibular protocol presents some limitations like the absence of feedback, no changes in the surface of work and lack of cognitive and task-oriented training; thus, vestibular training is based on repetitive exercises performed without a functional objective or variability in the environment [41,44]. Due to the intrinsic advantages of VRi and the multimodal design [108] of the protocol, the limitations of the Cawthorne-Cooksey training are expected to be overcome by providing extrinsic feedback (game score and multisensorial stimulation) during exercise execution, possibility of adding changes in surface and base of support during the performance, cognitive and task-oriented training (exergames), and avoiding humdrum exercise repetitions because of the motivational and enjoyable environment . [52,108]

Owing to VRi tracking (gyroscopes, accelerometers, and magnetometers) and software systems that record head and corporal movements in six degrees of freedom, it is possible to perform exercises in different postural circumstances, similar to our experimental protocol (sitting down, standing, single leg support, tandem, and standing on foam surface), ensuring virtual environment verticality.[78,109] Furthermore, the command centre of movements and multisensory stimulation are primarily found at the cephalic level in HMD, making VRi a suitable device for vestibular rehabilitation.[85,110–112] Moreover, current VRi devices are affordable, own high-resolution graphics, higher frames per second, less delay and latency, and accurate software and hardware.[113,114] These enhance the sense of presence and immersion of the subject and reduce the possible appearance of cybersickness, as confirmed by Weech et al.[115]

Clinical applicability of VRi vestibular rehabilitation

The Cawthorne-Cooksey intervention, on which our VRi protocol is based, has been demonstrated to be effective in several populations, such as elderly people,[108] people with vertebrobasilar insufficiency,[116] and those with benign paroxysmal positional vertigo.[117] Thus, arguably, vestibular VRi intervention based on this gold standard could be effective in the mentioned populations, including patients with MS. Prominsing previous studies have reported the effectiveness of VRi in vestibular rehabilitation for unilateral vestibular hypofunction,[46,48] Ménière disease,[43,44] and traumatic brain injury.[118] Moreover, a recent systematic review by Soltani et al.[119] supports HMD as a feasible and safe intervention to improve balance in older adults; because of this, we hypothesize that VRi vestibular intervention will be safe and feasible in MS population [120–123].

Finally, telerehabilitation strategies combined with VR have been poorly studied in the MS population.[124] A recent study with ten MS participants showed satisfactory results in balance and gait, but not for fatigue, after a telerehabilitation intervention based on Nintendo Wii exergames.[125] With regard to our protocol, because Oculus Quest is

wireless and portable, exercises can be performed at the laboratory, in public, in private clinics, and at home. In addition, this HMD has two features to ensure safety. The first is a restricted game zone to avoid blows, and on getting out, the real physical context will be displayed on the headset. Second, the virtual content of the session can be supervised through the Oculus app or via streaming, which is essential in telerehabilitation or home-based programs.[126]

Declaration of conflicting interests.

Authors of this papers declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

CGM, MDCV and MJCH conceptualised and designed the study. CGM wrote the first draft of the manuscript with critical input from MJCH. MDCV, MJCH, JCHR, EPP and RPC contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

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Table 1. Description of initial phase of vestibular intervention in both groups of study base on convectional protocol of Cawthorne- Cooksey exercises

Block of exercises	CG: Duration/ repetitions	CG intervention: Cawthorne- Cooksey protocol	EG intervention: adaptation of Cawthorne-Cooksey protocol to **virtual environments**	EG: Duration/ repetition
Sit down: eyes and head movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Stare a finger put in front of the face; move it closer and farther	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	24 minutes (combination of two blocks is performed because some exercises are answered by the same exergame) - Main room of First Steps: 11 minutes (10 slow repetitions and then 10 faster repetitions) - Shots in the Space: 7 minutes (all guns) - Beat saber:3 minutes (1 song) - Dance with
		2. Move the head to the right and the left, with open eyes	**First Steps: Main room and Shots in the Space**. Move and object in front of eyes and follow it + Shooting targets that appeared in the exergame
		3. Move the head up and down, with open eyes	**Shots in the Space (First Steps).** Shooting target that appeared randomly inside the virtual environment
		4. Look up and down while the head is fixed	**Beat Saber + Main room of First Step.** Cutting blocks with saber while head is fixed / hit a ball in the main room and fixated gaze on its movement while head is fixed
		5. Look to the right and left while the head is fixed	
		6. Repeat exercise 4 and 5 in close eyes condition	Not possible in virtual environment
Sit down: head and body movement	15 minutes Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Look an object placed in the floor. Then bring it above the head and place it again on the floor. Along all the movement look to the object.	**Main room of First Steps** Take a block from the virtual desk and bring to the floor and then above your head, while staring at it
		2. Shrink your shoulders and do circular movements	**Dance with Robot (First Steps)** Shrink shoulder while dancing with a Robot
		3. Bend forward and move an object around your knees	**Main room of First Steps** Bend forward and move a virtual block between the knees

				Robot: 3 minutes
Standing up exercises	15 minutes Each exercise will be performed 5 slow repetitions and then 5 faster repetitions	1. Sit down and stand up and vice versa with open eyes	**Beat saber**	21 minutes - Beat sabe: 3 minutes (1 song) - Baseball: 8 minutes - Tennis: 4 minutes - Bowling: 6 minutes
		2. Sit down and stand up and vice versa with close eyes	Not possible in virtual environment	
		3. Stand up moving to the right while standing	**Bowling (Sports Scrambles)** Stand up moving to the right or the left while taking a bowling ball	
		4. Stand up moving to the left while standing		
		5. In front of your face, throw a ball from one hand to the other	**Baseball/ Tennis (Sports Scrambles)** Throw or hit a ball in front of your face	
		6. Under the knee level, throw a ball from one hand to the other	**Bowling (Sports Scrambles)** Throw the ball to hit the bowls under the knee level	

Table 2. Description of advanced phase of vestibular exercises for both groups

Exercises for both groups	CG: Duration and frequency	Control group	Experimental group	EG: Duration and frequency
1. Changing from sitting to standing and vice versa	10 repetitions	From a situation of sitting in a chair stand up and throw a ball	**Main room of First Steps** Take a block from virtual desk and when the subject stands up throw it a virtual sign situated inside the virtual environment	10 repetitions
2. Move and throw an object from one hand to the other while standing with feet together. Staring all the time to the object.	10 repetitions moving the object 10 repetitions throwing the object	Move a ball at eyes level and then throw it from one hand to the other	**Main room of First Steps** Move a virtual block at eyes level Take a virtual block and throw it from one hand to the other	10 repetitions moving the object 10 repetitions throwing the object
3. 360º turn	10 repetitions to the right/left	Turn 360º degrees and throw a ball to a target	**Main room of First Steps** Take a virtual block, turn 360 º and throw it to a located target in the environment	10 repetitions to the right/left
4. Moving the head with narrow base of support	15 repetitions (Example: 1 repetition look to the right)	Move head to right and left with feet together	**Main room of First Steps** In standing position with narrow base of support hit a ball and follow with the head its movements	5 repetitions (Example: 1 repetition is until the ball stops)
5. Stare an object put in front of the face; move it closer and farther while standing on foam surface	10 slow repetitions 10 fast repetitions	Stare a small ball and move it closer or farther to your face	**Main room of First Steps** Take the pin-pong ball and put it in front of the face and move it closer and farther	10 slow repetitions 10 fast repetitions
6. Fast side head movements while standing on foam surface	15 repetitions	Throwing a ball to the right and left to the left while standing on a foam surface. Follow the ball with the head	**Main room of First Steps** Take the pin-pong racquet and hit blocks to one side and another following them with the head	15 repetitions

7. Move and object to the floor and bring it above your head while standing on a foam surface	10 repetitions	Taking a ball and make the exercise	**Main room of First Steps** Taking a virtual block from the desk perform the exercise	10 repetitions
8. Head movements while alternative single leg support	15 repetitions	Look to the right and the left while you maintain a monopodal balance	**Shots in the Space (First Steps)** Shooting targets just with one pistol, while single leg support	1 game
9. Head movements in a tandem position	15 repetitions	Look to one side and other while maintaining a tandem position	**Shots in the Space** Shooting targets with double gun while you maintain a tandem position	1 game
10. Head movements while standing on a foam surface	15 repetitions	Look to one side and other while standing on a foam surface	**Shots in the Space** Shooting targets with a machine gun while standing on a foam surface	1 game
11. Ocular movements with fixed head while standing on foam surface	20 repetitions (5 to right/left, 5 up/5 down)	Move eyes with fixed head while standing on a foam surface	**Beat Saber** Hit and cut blocks in a specific direction with sabers while standing on a foam surface	1 game
12. Throw a ball while standing on a foam surface	15 repetitions	Throw a ball to the physiotherapist and catch it again	**Baseball (Sports Scrambles)** Throw the ball in a baseball stadium while standing on a foam surface	1 game
13. Bowling with narrow base of support	10 repetitions	Bowl with feet together	**Bowling (Sports Scrambles)** Bowl with feet together	1 game
14. Bowling while standing on a foam surface	10 repetitions	Perform the exercise	**Bowling (Sports Scrambles)** Perform the exercise	1 game
15. Head movements while walking through a corridor	20 repetitions	Walk down a corridor while moving head	**Bowling (Sports Scrambles)** Walk down a bowling alley, while moving head side to side and the throw the bowling ball	2 games

Table 3. Primary outcomes pre-defined thresholds.

Feasibility measurements	**Measure**	**Pre-defined thresholds**
Recruitment/participation rate [85]	Proportion of potential participants who agree to complete screening and consent to participate	≥65%
Adherence rate [86]	Proportion of participants who attend and complete the intervention	≥80%
Retention rate [85]	Proportion of participants with complete study data at 3 and 6 months follow-up	≥75%
Usability [87,88]	SUS	≥60 points
Safety measurements		
Cybersickness [89]	SSQ	≤ 15 points
Fatigue to exercise [90]	ROF	≤ 4 points
Adverse events	Session's registry	No between groups differences

ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

Table 4. Data collection

Data and outcomes of study	Assessment details	Screening and recruitment	Baseline T0	During intervention	After intervention T1	Follow-up at 3 months T2	Follow-up at 6 months T3
Eligibility assessment		X					
Demographic variables		X					
Feasibility	Recruitment rate Adherence rate Retention rate Usability: SUS Individual semi-structured interview				X		
Safety	Cybersickness: SSQ Fatigue to exercise: ROF Falls/ adverse events registry			X			
Dizziness	DHI		X		X	X	X
Static Balance	Biodex Balance System: Length, antero-posterior, mediolateral sway, and velocity of centre of pressure. Open and close eyes condition. Firm or foam surface.		X		X	X	X
Dynamic Balance	BBS		X		X	X	X
Fatigue	MFIS		X		X	X	X
Quality of life	MSQoL-54		X		X	X	X

DHI: Dizziness Handicap inventory; BBS: Berg Balance Scale; MFIS: Modified Fatigue Impact Scale; MSQoL-54: Multiple Sclerosis Quality of Life- 54; ROF: Rating-of-Fatigue; SSQ: Simulator Sickness Questionnaire; SUS: System Usability Scale.

FIGURES LENGEND

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc. 1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

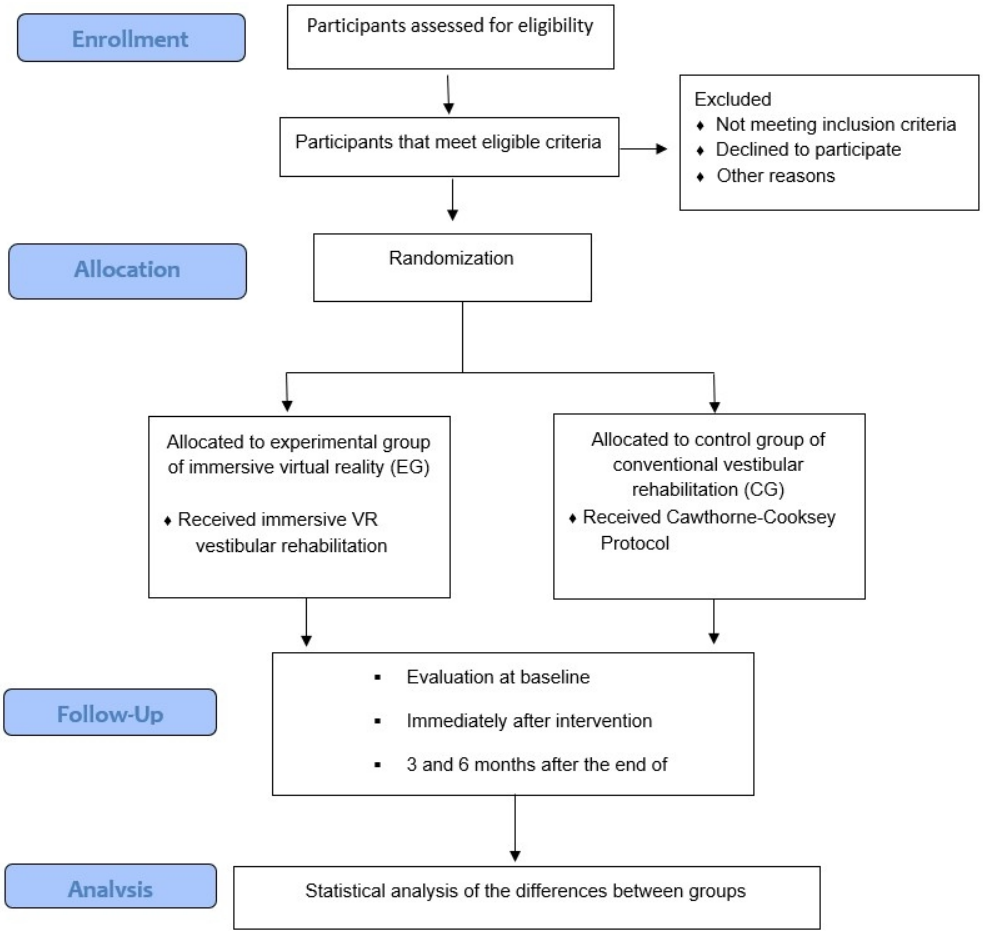

Figure 1. The CONSORT Flow Diagram of the participants recruitment and progress through the phases of the trial.

169x157mm (120 x 120 DPI)

Figure 2. Virtual environments of exergames from the VRi vestibular rehabilitation. Oculus Quest. Facebook, Inc. 1. Main room of First Steps 2. Dance with Robot 3. Shots in the Space 4. Beat Saber 5. Tennis (Sport Scrambles) 6. Baseball (Sport Scrambles) 7. Bowling (Sport Scrambles)

219x154mm (120 x 120 DPI)

Model Informed Consent Form

Study Title*:* **Feasibility and safety of an immersive virtual reality-based vestibular rehabilitation program in people with multiple sclerosis experiencing vestibular impairment: A protocol for a pilot randomised controlled trial**

Principal investigator: Cristina García Muñoz

Organization: University of Seville

This informed consent is formed by two parts:

I. **Information sheet**
II. **Certificate of Consent**

A copy of this form will be provided to you, in order you can take as much time as you need to make the final decision.

Part I: Information sheet

A. Introduction

This informed consent form is for people with multiple sclerosis who suffer from dizziness, vertigo or imbalance. We are inviting you to participate in the research driven by our research team at the Physical therapy Department of the University of Seville (Spain). The current research was reviewed and approved by the Andalusian Review Board and Ethics Committee Virgen Macarena-Virgen del Rocio Hospitals (ID 2148-N-19, 25th March 2020). This study complies with the Helsinki Statement. The aim of this form is to provide you with enough information to help you in your participation decision. Please, before you decide, read the information below carefully and feel free to ask the investigator if you have any question. The information will help you to understand the objective of study, procedures and duration and the possible benefits or risk derived from the research.

B. Background

Dizziness, balance disorders and fatigue are common clinical manifestation in multiple sclerosis (MS) having a direct impact in quality of life. Dizziness could affect between of 49-59 % of MS patients, and it is highly related to imbalance. This problem could have a peripheral or central vestibular origin in this population. Thus, MS population could be benefit from a vestibular rehabilitation program. Major goals of vestibular rehabilitation are to decrease symptoms of dizziness, improve ocular fixation, improve stability and its effects on daily living activities. Immersive virtual reality (VRi) is a booming tool in vestibular and neurorehabilitation because of its added advantages. However, VRi has obtained promising results reducing dizziness and improving balance in patients with peripheral vestibular disorders, no previous studies can be found in MS. That is why it is necessary to examine the feasibility and safety of the VRi as a vestibular rehabilitation intervention to improve dizziness, balance, fatigue, and quality of life in people with multiple sclerosis. Both groups of study will receive the same intervention with the only difference of the performance of the exercises trough the VRi device. This study purposes a VRi intervention based on the gold standard vestibular protocol Cawthorne-Cooksey. Improvements of symptoms will have a direct repercussion in the quality of life of MS

patients. To examine these effects, up to 30 participants may join the experimental intervention purpose in this research applying a seven week intervention period.

C. Purpose of study

To assess feasibility and safety of the experimental VRi vestibular protocol.

To examine the changes in dizziness, balance, fatigue and quality of life after a VRi vestibular protocol compared to conventional vestibular rehabilitation.

Procedure

Your participation in this research is completely voluntary. Experimental intervention will not have any cost to you. If you decide to reject your participation, once you have singed the informed consent form, you are entirely free to do it. You only must notify your desire to the principal investigator. You will not be required to give reasons for your decision to leave the research process. No ethics or economics conflicts will be carried out because of your rejection to participate. If you are willing to participate, before you enrolled the study you need to sing this informed consent form. Before you start with therapy you will participate in a baseline assessment drive by a physical therapist trained in vestibular rehabilitation. This initial evaluation will take place at Physiotherapy Department of the University of Seville. This initial assessment is constituted by:

- Dizziness Handicap Inventory (DHI): is a self-assessment questionnaire of 25 items. The aim of DHI is to evaluate the impact of dizziness on the quality of life. Higher scores of the questionnaire means more impact of dizziness in quality of life.
- Static balance will be evaluated by the Biodex Balance System. The mentioned balance system allows registration of the location of the centre of pressure.
- The Berg Balance Scale (BBS) is the selected instrument to measure dynamic balance. BBS is constituted by 14-items, each ranging from 0 (cannot perform) to 4 (normal performance), where higher values indicate better dynamic balance.
- Modified Fatigue Impact Scale (MFIS): self-reported questionnaire that evaluates the perceived impact of fatigue in MS patients. This scale is composed of 21-items which assess fatigue impact in three different domains.
- Multiple Sclerosis Quality of Life Scale 54 (MSQoL-54): This is a 54-item questionnaire distributed into 12 multi-item scales. The overall score range is from 0 to 100 scales. Higher values indicate better quality of life

Once the baseline assessment ends, vestibular rehabilitation will be administered by a qualified physical therapist.

During sessions, physical therapist will be near to you to avoid possible falls. If any falls or another adverse event occurs during session it will be register by the therapist. To assess the possible appearance of Cybersicknes (nausea, dizziness, vomitus due to the VRi) Simulator Sickness Questionnaire will be provided to you by the therapist.

- Simulator Sickness Questionnaire (SSQ): The SSQ consists of a 16-item questionnaire divided into 3 categories: nausea, oculomotor and disorientation. Scores ranging between 10 and 15 mean significant symptoms, and above 20 indicates a simulator problem.

- Rating-of-Fatigue Scale (ROF): It is employed to quantify fatigue during the performance of exercise. This scale is a visual analogue rating scale ranging from 0 (non-fatigue) to 10 (totally fatigued/exhausted).

Once the intervention ends you will return to the University of Seville for a post-intervention revaluation in which same test and questionnaires will be provided to you. Only System Usability Scale will be new in the evaluation process.

- System Usability Scale (SUS): SUS is a 10-item questionnaire in which participants consider their perception of the VR device usability using a 5-point Likert scale, where 0 means strongly disagree and 5 means strongly agree. The overall score can range from 0 to 100.

Also, a semi-structured interview will be carried out individually after the end of intervention to know main perception and impression experienced by participants during the experimental training.

A reassessment 3 and 6 month after the end of the intervention will be carried out at the University.

D. Study design

This study is a randomised control clinical trial in which is compared two different interventions each one in a defined group. The participants' allocation will be randomised into experimental group and control group. Evaluators will be blinded to intervention and group assignation; this is known as single-blind. Both groups will receive a total of 20 session based on gold standard protocol of Cawthorne-Cooksey. Is necessary to compare an immersive virtual reality intervention (VRi) to Cawthorne-Cooksey to know the real effects and possible benefits associated to virtual reality. Specialist vestibular physical therapist will monitor and supervise sessions.

- Control group intervention: Gradual exposition to vestibular exercises will be provided by 10 initial session and 10 advanced. Each session will last 50 minutes with 5 minutes of rest at the middle of the session. Session will be performed 3 times per week along 7 weeks. Vestibular exercises will be the same in both groups based on the conventional Cawthorne-Cooksey vestibular training.
- Experimental group: Same frequency and duration of intervention will be carried out in the experimental group. Also, vestibular exercises based on Cawthome-Cooksey will be the same in both groups. The main difference in the experimental groups consist of the performance of exercises through the Oculus Quest system. Oculus Quest is a head mounted display through you can interact with a virtual reality environment. Exercises will be adapted to be execute in the virtual environment provided by exergames called: *First Steps, Beat Saber* and *Sport Scrambles*. Exergames can be defined as the videogame which allows to reproduce immediately external actions of the subject to the virtual world.

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E. Duration

The study starts at baseline assessment followed by administration of 20 session along 7 weeks. Once the intervention ends: DHI, Biodex Balance System, BBS, MFIS, MSQoL-54 VDAL, and SUS will be assessed and filled once more to examine the possible changes of outcomes. Reassessment will be made 3 and 6 months after the end of intervention. We will ask you to meet you at the University, 4 times in total owe to the evaluation process. Your participation in the research take place over 9 months in total.

F. Benefits

After the experimental intervention dizziness, balance, fatigue, and quality of life may improve or be resolved.

Risks

The participation on this study may involve the following risk:

- Possible apparition of pain in extremities derived from the physical exercise
- Slight possibility of transient nausea or dizziness
- Appearance of cybersickness during the performance of exercises through Oculus Quest.
- Possible falls. To reduce this possibility your participation will be supervised by the physical therapist.

G. Reminders and responsibilities

- Notify the research team if you wish to leave the study
- Follow the instructions given by investigators to achieve homogeneous course of the intervention
- Ask investigators if you any doubt or you do not understand something
- Tell investigators if you experience health changes during the research

H. Confidentiality

The information collect from the study will be kept confidential. Considering to data protection law you can modified or deny the access to them getting in touch to the principal investigator. Your personal data (name, age, address…) will be registered in a database in the Spanish Data Protection Agency. All your data will be codified by a number (in step of your name for example) known only by researchers. The research team is the only one authorized to manage your personal data through a confidential password. Your data will not be disclosed to third parties without your consent.

I. Sharing the results

Results from the study will be share in Scientifics conference or meetings. Furthermore, the study results will be disseminated via publication in peer-reviewed scientific journals. Private or confidential information will not be published or shared.

J. Conflict of interest

Authors of this paper declared no potential conflicts of interest respect to the research. The research team only is interested in completing this study. The investigators interest should not affect your consideration for participating.

K. Right to Refuse or Withdraw

This is a reconfirmation that you are completely free to accept or decline the offer to participate in this study. Also, you are entirely free to leave the research at any point without giving reasons.

L. Questions about the study

If you have any questions or doubts about the research (before, during or after the study) or you would like to speak to the research team, please contact to the main investigator: physical therapist Cristina García (+34) 954 55 14 71.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand that I am entirely free to leave the study at any moment after informing the principal investigator. I promised to follow the team research indications as much as possible. I know the possible benefits or risk derived from the experimental intervention. A signed and dated copy of the informed consent form will be given to me. I agree voluntarily to participate as a participant in the research titled: Feasibility of an immersive virtual reality-based vestibular rehabilitation program for dizziness, balance, and fatigue improvement in people with multiple sclerosis: pilot randomised controlled study

Patient signature: _____ Date: _____

I have provided a detailed information of the study to the participant including the possible benefits and risks. I have witnessed the accurate reading of the consent form to the potential participant. I have answered all doubts of the participant related to the research. I confirm that the individual has given consent freely.

Investigator signature: _____ Date: _____

Decline participation

I have read the foregoing information, or it has been read to me. After reading the information sheet any question I had have been answered to my satisfaction. I understand

that I am entirely free to leave the study at any moment after informing the principal investigator. Although, I refuse to participate in the research proposed in this informed consent form.

Patient signature: _____ Date: _____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,13
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4,5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8 + Table 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_Table 3,10____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_Table 3, 8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___5_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___6_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___6_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___8,10_____ __
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__8_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8,11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,11
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.