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

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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 (VRi) could also be implemented within a vestibular rehabilitation intervention.

Methods and analysis This protocol describes a parallel-arm, pilot randomised controlled trial, with blinded assessments, in 30 patients with MS with vestibular impairment (Dizziness Handicap Inventory ≥16). The experimental group will receive a 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 7 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, 25 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 NCT04497025.

Strengths and limitations of this study

- As the immersive virtual reality (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, having repercussions 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 is a myriad of vestibular system disorders, which could have a peripheral (inner ear, vestibular nerve) or 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 vestibulospinal 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 while 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, decreasing dizziness, improving ocular fixation and stability, and having better 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 as 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 already been proven.[51] Moreover, a systematic review found that immersive VR (VRi) presents additional clinical benefits when compared with 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] while the subject is exposed to a large variety of environments boosting the vestibular mechanism of habituation.[37 62] VRi allows the subject to complete immersion within the 360° virtual environment, enhancing the feeling of presence.[50 63 64] To the best of our knowledge, no previous research on VRi and vestibular rehabilitation in MS has been performed.

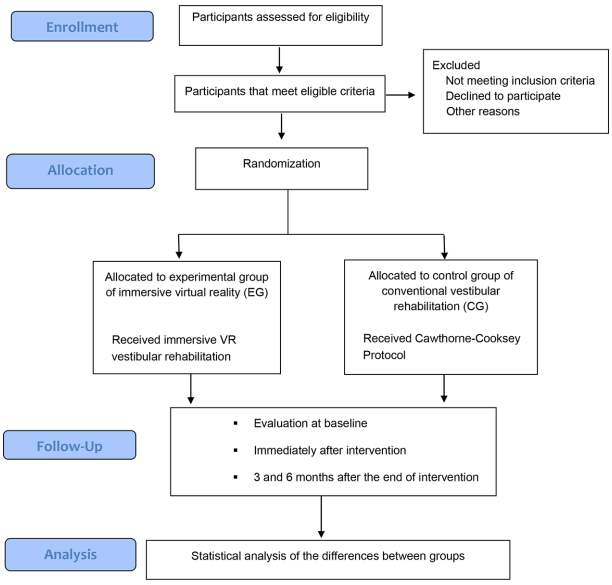

Figure 1 The Consolidated Standards of Reporting Trials flow diagram of the participants' recruitment and progress through the phases of the trial.

Therefore, the primary purpose of this study is to determine the feasibility and safety of a VRi-based vestibular rehabilitation programme in MS population. Second, we aim to preliminarily evaluate the preliminary 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 group (EG) and control group (CG). 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.[65] This RCT will also be developed following instructions from the Consolidated Standards of Reporting Trials.[66]

Study setting

The trial will be conducted at the Physical Therapy Department of the University of Seville (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 who 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 online 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 EDSS 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.[67] 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)[68] or balance problems (Berg Balance Scale (BBS) ≤47).[69] 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 neurological disorder contributing to balance impairment.
- Disease relapse within the last 3 months (transitory exacerbation of the disease by the appearance of neurological clinical manifestations: imbalance, dizziness and more).[27 70 71]
- 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 members of the 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 semistructured interview process for each participant will be included. This triangulation method will help us to interpret the study findings.[72]

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

Interventions

Conventional vestibular rehabilitation protocol (control group)

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 improve vestibular compensation through a mechanism of neuroplasticity, known as adaptation, habituation and substitution.[37 62 73] 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.[74 75] 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 10 sessions, they will begin with more complex exercises. To develop these advanced vestibular exercises for both groups, the principles and keys of Cooksey,[31] Han *et al*[37] and Whitney and Sparto[62] were assumed. The advanced phases of the intervention for participants in the CG are described in table 2. This intervention matches the EG, with the only

Table 1 Description of initial phase of vestibular intervention in both groups of study based 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 min Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Stare at a finger put in front of the face; move it closer and farther	**Main room of First Steps** Take the ping-pong ball and put it in front of the face and move it closer and farther	24 min (combination of two blocks is performed because some exercises are answered by the same exergame) ► Main room of First Steps: 11 min (10 slow repetitions and then 10 faster repetitions) ► Shots in the Space: 7 min (all guns) ► Beat Sabre: min (1 song) ► Dance with Robot: 3 min
		2. Move the head to the right and the left, with open eyes	**First Steps: main room and Shots in the Space** Move the 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 Sab re+main room of First Step** Cutting blocks with sabre 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 closed eyes condition	Not possible in virtual environment	
Sit down: head and body movement	15 min Each exercise will be performed 10 slow repetitions and then 10 faster repetitions	1. Look at 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 min 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 Sabre**	21 min ► Beat Sabre: 3 min (1 song) ► Baseball: 8 min ► Tennis: 4 min ► Bowling: 6 min
		2. Sit down and stand up and vice versa with closed eyes	Not possible in virtual environment	
		3. Stand up moving to the right while standing	**Bowling (Sports Scramble)** 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 Scramble)** 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 Scramble)** Throw the ball to hit the bowls under the knee level	

CG, control group; EG, experimental group.

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 with 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 programme will be conducted by an experienced vestibular rehabilitation physical therapist, who will provide verbal indications and stay near the

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

Exercises for both groups	CG: duration and frequency	CG	EG	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 eye level and then throw it from one hand to the other	**Main room of First Steps** Move a virtual block at eye 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. 360° turn	10 repetitions to the right/left	Turn 360° and throw a ball to a target	**Main room of First Steps** Take a virtual block, turn 360° 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 (eg, 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 (eg, 1 repetition until the ball stops)
5. Stare at an object put in front of the face; move it closer and farther while standing on a foam surface	10 slow repetitions 10 fast repetitions	Stare at a small ball and move it closer or farther to your face	**Main room of First Steps** Take the ping-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 a foam surface	15 repetitions	Throwing a ball to the right and left while standing on a foam surface. Follow the ball with the head	**Main room of First Steps** Take the ping-pong racket and hit blocks to one side and another following them with the head	15 repetitions
7. Move an 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 the 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 the 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 a foam surface	20 repetitions (5 to right/left, 5 up/5 down)	Move eyes with fixed head while standing on a foam surface	**Beat Sabre** Hit and cut blocks in a specific direction with sabres 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 Scramble)** 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 Scramble)** Bowl with feet together	1 game
14.Bowling while standing on a foam surface	10 repetitions	Perform the exercise	**Bowling (Sports Scramble)** Perform the exercise	1 game

Continued

Table 2 Continued

Exercises for both groups	CG: duration and frequency	CG	EG	EG: duration and frequency
15.Head movements while walking through a corridor	20 repetitions	Walk down a corridor while moving head	**Bowling (Sports Scramble)** Walk down a bowling alley, while moving head side to side and then throw the bowling ball	2 games

CG, control group; EG, experimental group.

participants to lend them confidence and decrease the risk of falling during the session.

VRi 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 360° virtual environment and enables interaction. Immersive virtual 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 with 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.[76 77]

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 is described in table 1. In the initial phase, the advanced phase exercises will be the same in both groups, with the main difference being the interaction with the immersive virtual environment. The advanced 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 Sabre demo and *Sports Scramble 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, ping-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 Sabre* is a rhythm music game in which blocks are slashed in a specific direction with a red (left hand) and blue (right hand) sabre, while trying to avoid some obstacles. *Sports Scramble* consists of three sports games: baseball, tennis and bowling, in which one must defeat their opponent while balls, rackets or your baseball bat is 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, semistructured interviews will be conducted with the VRi intervention

Figure 2 Virtual environments of exergames from the VRi vestibular rehabilitation, Oculus Quest, Facebook. (1) Main room of First Steps; (2) Dance with Robot; (3) Shots in the Space; (4) Beat Sabre; (5) Tennis (Sports Scramble); (6) Baseball (Sports Scramble); (7) Bowling (Sports Scramble). VRi, immersive virtual reality.

Table 3 Primary outcomes' predefined thresholds

Feasibility measurements	Measure	Predefined thresholds
Recruitment/participation rate[84]	Proportion of potential participants who agree to complete screening and consent to participate	≥65%
Adherence rate[85]	Proportion of participants who attend and complete the intervention	≥80%
Retention rate[84]	Proportion of participants with complete study data at 3-month and 6-month follow-up	≥75%
Usability[86 87]	SUS	≥60 points
Safety measurements		
Cybersickness[88]	SSQ	≤15 points
Fatigue to exercise[89]	ROF	≤4 points
Adverse events	Session's registry	No between-group differences

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

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 VR treatment and a registry of falls and other adverse events. Predefined thresholds for considering the feasibility and safety of the VRi intervention are described in table 3.[78–83]

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 VR 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.[80 81] 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 is a 16-item questionnaire divided into three categories: nausea, oculomotor and disorientation.[84 85] Scores ranging between 10 and 15 indicate significant symptoms, and those above 20 indicate a simulator problem.[82] 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).[83] 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.[86–88] This instrument is reliable and valid for the study population.[89 90] The minimal clinical importance difference (MCID) has been established at 18 points in patients with vestibular disorders.[88]

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).[91–93] Biodex has been proven to be a valid instrument for evaluating stability and postural control in subjects with MS.[94 95] Moreover, Biodex can compute the following variables in relation to the CoP:

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

Each variable will be assessed in open or closed eyes condition and on a 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.[96 97] This assesses the skills of sitting, standing, leaning, turning and standing on a monopodal support. The BBS has proven to be reliable and valid for the study population.[89 90] The MCID for BBS has been set at 3 points for people with MS by Gervasoni *et al*.[98]

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.[99 100] This scale is reliable and valid for measuring the impact of fatigue in patients with MS.[101 102] The MCID for MFIS has been established at 19.23% by Rietberg *et al*[103] and 4 points by *Roony et al*.[104]

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 will be used.[105] 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.[106]

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.[76] 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,[76 77] 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 predefined 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±SD or as percentages. Similarly, for non-normal distribution, median, minimum and

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 semistructured 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, anteroposterior, mediolateral sway and velocity of centre of pressure. Open and closed 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

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

maximum values, and IQRs will be reported. Baseline differences between groups will be analysed using the X^2 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 (V.25.0; IBM Corp) and GraphPad PRISM (GraphPad, San Diego, California, 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, 25 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[107] 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.[52 107]

Owing to VRi tracking (gyroscopes, accelerometers and magnetometers) and software systems that record head and corporal movements in 6 df, 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.[77 108] 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.[84 109–111] Moreover, current VRi devices are affordable, own high-resolution graphics, and have higher frames per second, less delay and latency, and accurate software and hardware.[112 113] These enhance the sense of presence and immersion of the subject and reduce the possible appearance of cybersickness, as confirmed by Weech *et al*.[114]

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,[107] people with vertebrobasilar insufficiency[115] and those with benign paroxysmal positional vertigo.[116] Thus, arguably, vestibular VRi intervention based on this gold standard could be effective in the mentioned populations, including patients with MS. Promising previous studies have reported the effectiveness of VRi in vestibular rehabilitation for unilateral vestibular hypofunction,[46 48] Meniere's disease[43 44] and traumatic brain injury.[117] Moreover, a recent systematic review by Soltani and Andrade[118] supports HMD as a feasible and safe intervention to improve balance in older adults; because of this, we hypothesise that VRi vestibular intervention will be safe and feasible in MS population.[119–122]

Finally, telerehabilitation strategies combined with VR have been poorly studied in the MS population.[123] A recent study with 10 participants with MS showed satisfactory results in balance and gait, but not for fatigue, after a telerehabilitation intervention based on Nintendo Wii exergames.[124] 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 one 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 programmes.[125]

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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.

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 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: _____