End-Of-Term Project

Vestibular rehabilitation through Cave Automatic Virtual Environment versus traditional physical therapy to improve balance in patients with multiple sclerosis.
A multicenter randomized controlled trial.

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Girona, January 2018

I would like to sincerely thank the warm support, advice and dedication received from the neurology team at Figueres hospital especially from Dra. Olga Carmona during all stages of this project.
Thank you very much for making this project a reality and for making me love neurology in all its aspects.

Thank you Dr. Abel Lopez for helping me in the methodological and statistical part of this project.

«Success is the ability to go from failure to failure without losing your enthusiasm »
-Winston Churchill (1874 – 1965) -

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GLOSSARY

- MS Multiple Sclerosis
- CNS Central Nervous System
- CIS Clinically Isolated Syndrome
- MRI Magnetic Resonance Imaging
- RRMS Relapsing-Remitting Multiple Sclerosis
- SPMS Secondary Progressive Multiple Sclerosis
- PPMS Primary Progressive Multiple Sclerosis
- CSF cerebrospinal fluid
- QoL Quality of Life
- DLA Daily Life Activities
- VR Vestibular Rehabilitation
- HRQoL Health Related Quality of Life
- CAVE Cave Automatic Virtual Environment
- HF Hospital de Figueres
- HUGDJT Hospital Universitari de Girona Dr Josep Trueta
- HGTP Hospital Germans Trias I Pujol
- BBS Berg Balance Scale
- EDSS Expanded Disability Status Scale
- TGUG Test Get Up and Go
- 2MWT Two Minute Walk Test
- SF-36 Short Form-36 Questionnaire
- ZBI Zarit Burden Interview

1. ABSTRACT

Background: *Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS), it affects mainly women, and usually occurs in young adults. Balance impairment is one of the initial and most common causes of severe disability in MS patients, it contributes significantly to reducing the patient mobility and risk of accidental falls, the patient independence and the ability to perform daily life activities (DLA).*
MS has no cure, treatments currently available aim to reduce relapses and delay the progressive worsening of the disability. Therefore, management of MS patients is based on a multidisciplinary approach in which traditional physical therapy is widely used and aims to enable patients to live better their disease. Recently, vestibular rehabilitation (VR) based on cave automatic virtual environment (CAVE) has been introduced as a relevant novelty in the physical and psychological rehabilitation of neurological diseases, especially for gait and balance impairment.

Objectives: *This study aims to compare the efficacy of VR through CAVE with traditional physical therapy to improve balance in MS patients. In addition, efficacy on the risk of falls, gait, patient and caregiver quality of life (QoL), disability progression and cost-effectiveness will be analyzed.*

Design: *We designed a multicenter randomized clinical trial, where we will select a total of* ***206*** *individuals. The reference center for this trial will be the Hospital de Figueres, although collaboration and coordination will be required from both the Hospital Universitari de Girona Dr. Josep Trueta and the Hospital Germans Trias i Pujol to obtain the necessary sample.*

Methods: *By randomization, we will allocate equally the participants in 2 groups, one group will receive VR through CAVE and the other group will receive traditional physical therapy exercises. We will report any complications that may occur during or after the intervention. For the statistical analysis of balance improvement obtained with each therapy, Chi-square test will be used in case of parametric data, and Fisher exact test in case of non-parametric data.*

Participants: *Men and women aged from 18 to 50 years old with a confirmed diagnosis of relapsing remitting MS (RRMS), balance impairment according to the Berg Balance Scale (BBS) and Expanded Disability Status Scale (EDSS) score between 3 and 5.*

Keywords: *Multiple sclerosis, Randomized clinical trial, Vestibular rehabilitation, Cave automatic virtual environment, Physical therapy exercises, Balance, quality of life.*

2. INTRODUCTION

2.1. Definition

Multiple sclerosis (MS) is a chronic autoimmune, demyelinating, inflammatory, and progressive disease that affects the entire central nervous system (CNS), characterized by the disturbance of the nerve pathways function, causing disorders in motor, sensory, visual, urinary, cognitive, balance and coordination functions (1), an important interference with the family, work and social environment (2), and a high economic burden on the National Health System (3,4).
MS is the main cause of non-traumatic chronic disability in young adults, affecting more frequently women with an average age of 30 years (5). The most common form of presentation is the relapsing-remitting form that represents about 80 to 90% of all MS patients, it can evolve to more progressive forms. About 10 to 20% of MS patients present the primary progressive form with continuous progression of signs and symptoms and without relapses (1).

2.2. Epidemiology

It is estimated that more than 2.1 million people around the world are affected by MS (2). In Spain the prevalence ranges from 79 to 125 cases per 100.000 inhabitants (6), although there is an important variability according to each region (7). It is 3 times more frequent in women than in men and it starts mainly between 20 and 50 years old with an onset average age of 30 years (5).

2.3. Risk factors

MS is a multifactorial disease, in which environmental, genetic and immunological factors are involved. Although being usually sporadic, several genetic studies have demonstrated familial aggregation in MS and more occurrence in relatives of patients with this disease than in the general population with about a 30% concordance rate among monozygotic twins (5). The implication of factors from the HLA Class II region of the Major Histocompatibility Complex (MHC) has been clearly established since many years, specifically the HLA-DRB1 * 1501 allele on chromosome 6p (5,8). Epigenetic factors like DNA methylation (9), non-coding RNAs and histone modifications are also demonstrated as well as the IL-2Ra, IL-7Ra, a TNF receptor and a tyrosine kinase genes (10).

The involvement of environmental factors in the onset of MS could be demonstrated by many epidemiological studies especially tobacco (11), viral infectious factors such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Overweight/obesity, early-life hygiene, nutritional, Vitamin D and sun exposure deficiencies during childhood and absence of breastfeeding during infancy are factors that have an association with increased risk of developing the disease (8,12,13,14).

2.4. Pathophysiology

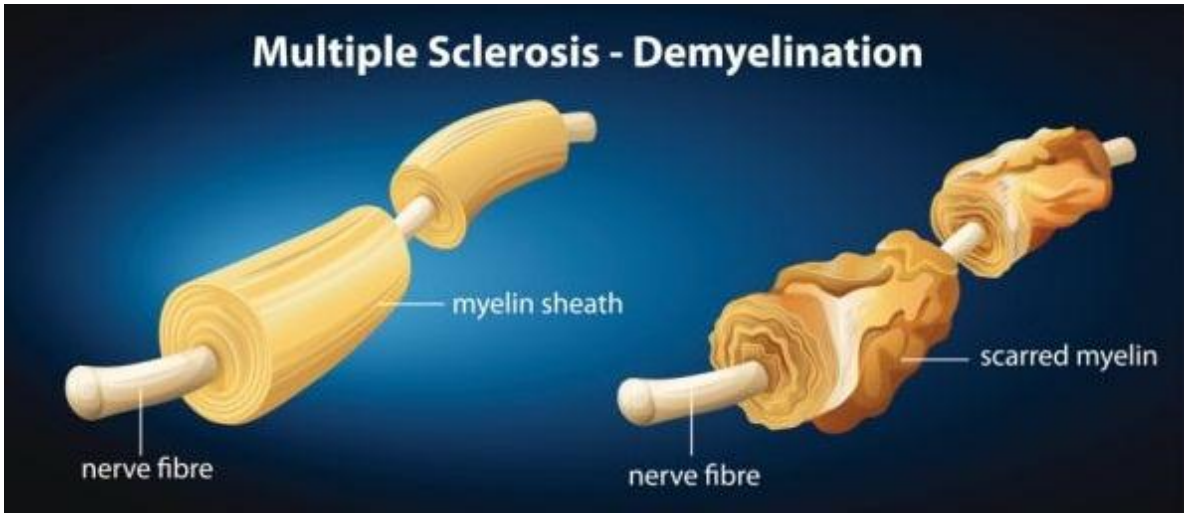
a- Immunological aspects

MS is suspected to be caused by induced inflammatory lesions in which CD8+ T cells and CD4+ T cells and activated microglia and macrophages are the main actors. Activated macrophages and microglia release excitotoxins, cytotoxic cytokines, reactive oxygen and nitric oxide species that cross the blood-brain barrier and damage oligodendrocytes, neurons and myelin sheath highly vulnerable to these products. Other more important demyelination patterns include hypoxia-like tissue injury, antibodies and complement-associated changes (15).

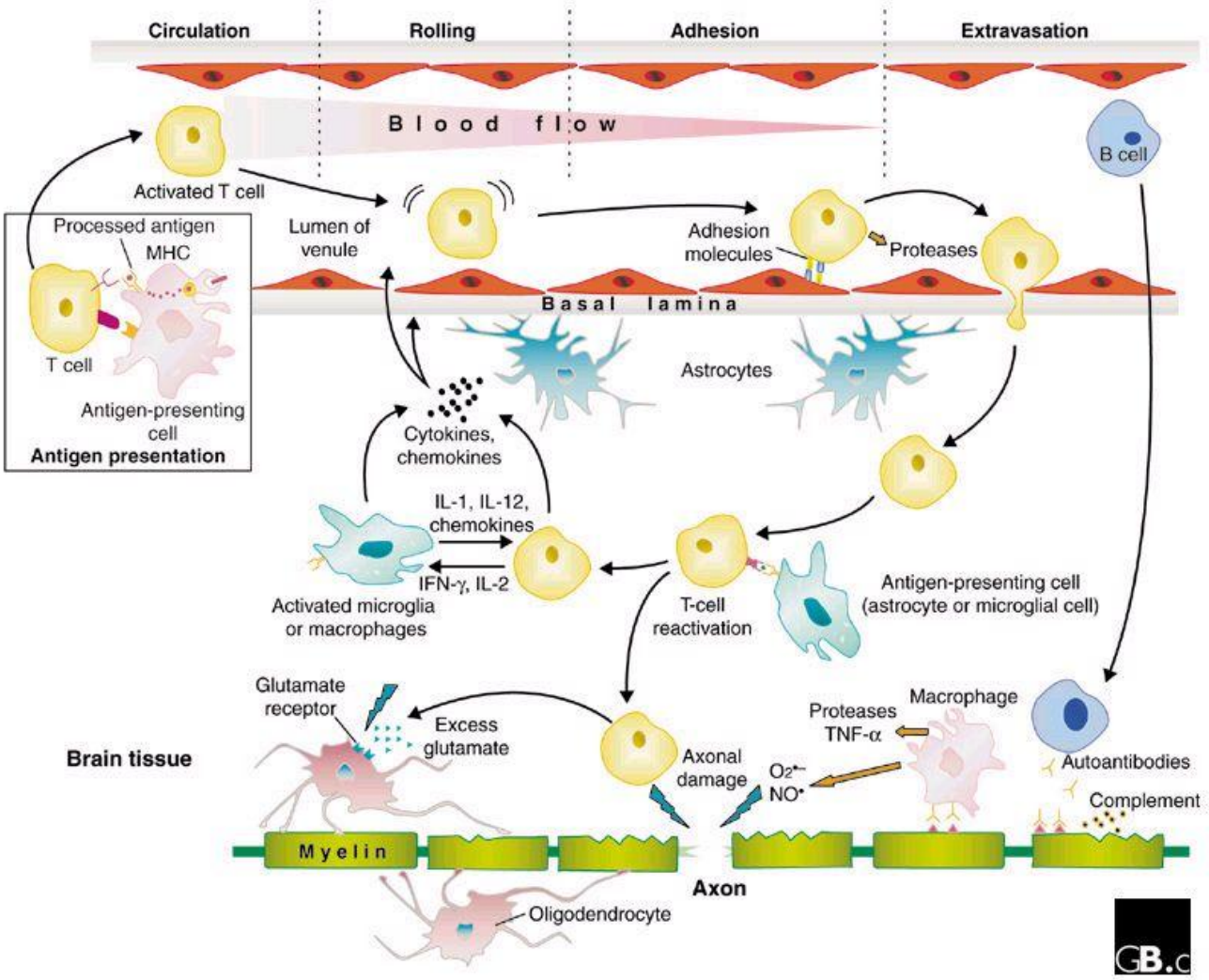
b - Histological aspects

*** Demyelination:** related to the inflammatory process in the CNS, although several pathogenic demyelination mechanisms may act in different subgroups of patients with MS. The myelin loss is the cause of impaired conduction of the nervous impulse, and the demyelination focus are dispersed throughout the CNS with formation of cortical plaques (16).
If lesions are still early, they may progress to remyelination, a spontaneous process of regeneration after demyelination that decreases with age and progression of the disease, otherwise disequilibrium between demyelination and remyelination courses and permanent progression to established sclerosis occurs with neuronal loss and axonal degeneration (17).

*** Axonal degeneration:** related to Macrophage-associated toxic molecules, glutamate and Nitric oxide, it represents the permanent functional disability and can occur in both inflammatory and chronic lesions. It is mainly a consequence of demyelination and it marks the irreversible character of the disease (16).



https://www.quora.com/What-is-Demyelination-What-are-Symptoms



http://www.mult-sclerosis.org/news/Oct2002/FullTextLargeScaleGeneExpressionStudiesOfMS.html

2.5. Symptoms and clinical phenotypes

The global evolution and prognosis of MS are heterogeneous and have highly variable clinical manifestations (18). Some patients have a completely benign MS without disability, while others are confined to the wheelchair or to bed due to a severe form of the disease (19).

The first episode of neurological dysfunction is called Clinically Isolated Syndrome (CIS) and frequently starts as a brainstem syndrome, partial myelitis or an acute optic neuritis, nevertheless it can affect any part of the CNS. After 20 years of follow-up, 82% of patients with CIS and an alteration in cerebral magnetic resonance imaging (MRI) develop clinical MS (1).

The most frequent symptoms in MS are the following: (15,20,21)

Affected area	Symptoms
Brainstem Cerebellum Vestibular system	Diplopia Spasticity Dysarthria Imbalance Headache Gait ataxia Vertigo ● acute vestibular syndrome ● positional vertigo
Spinal cord	Paresthesia Numbness Fatigue and weakness Pain Lhermitte's symptom Impotence and sexual dysfunction Constipation Bladder and bowel dysfunction ● overactive bladder ● detrusor- sphincter dyssynergia
Brain hemispheres	Sensitivity disorders Heat sensitivity Memory disorders Personality disorders Cognitive impairment Depression
Optic nerve	Blurry vision

There are 3 major clinical forms of MS:

- **Relapsing-remitting multiple sclerosis (RRMS)**: the most frequent, affecting approximately 80 to 90% of patients with MS, and it manifests by acute or subacute episodes, spaced in time with neurological deficit and partial or total improvement leaving or not sequels (1,22).
- **Secondary progressive multiple sclerosis (SPMS):** occurs after about 25 years of evolution of RRMS (90% of all RRMS patients), and it manifests as a progressive clinical worsening of neurological deficits and intensification of symptoms, although some patients may experience relative stability periods (22).
- **Primary progressive multiple sclerosis (PPMS):** approximately 10 to 20% of patients with MS

have a continuous progression of disability from the onset with association to severe impairment of motor functions, and a slow and insidious aggravation of the disability and without remission phases. It affects mainly the spinal cord with a progressive decrease of the cross-sectional area of the cervical region (23).

About 1% of patients may present occasional exacerbations after one or more symptoms at the time of the disease onset (progressive relapsing form) (20).

2.6. Balance in MS

Balance loss and impaired gait are caused by different factors that interact with each other, including spasticity, ataxia, weakness, fatigue, attention deficit, delay in somatosensory conduction and central integration lack of information. In addition, decreased walking speed can be caused by performing cognitive functions while walking, which can lead to falls and injury to the patient (24) Maintaining balance is a complex function that depends primarily on the proprioceptive signals from muscles, tendons, skin, joints, visual and vestibular systems that flow to the CNS. In people with MS, the important damage caused by the disease to CNS can reduce the ability to process afferent proprioceptive signals, leading to impaired postural response and poor balance maintenance. Balance disorders are a common symptom in patients with MS and represent a big part of disability caused by this disease, indeed, progressive impairment of static and dynamic equilibrium represents an important symptom of disease progression. Moreover, patients with MS may have altered balance even long before the onset of manifest clinical disability. For this reason, in MS people, it is extremely important to detect any change in balance with the aim to examine the disease progression and assess the possible positive effects of therapy (25).

2.7. Diagnosis

MS don't have an exclusive pathognomonic diagnostic test or clinical characteristic, the diagnosis is mainly a clinical, and based on clinical history, neurological examination, laboratory testing and evidence of CNS lesions. To confirm the diagnosis, MRI, the study of the evoked potentials (EP) and the cerebrospinal fluid analysis (CSF) are mainly used (26). According to the McDonald criteria, the diagnosis is based on demonstration of dissemination in space (1 or more T2 lesion in two or more areas of the CNS) and dissemination in time (a new T2 lesion and/or gadolinium-enhancing lesions on MRI, or asymptomatic gadolinium-enhancing and non-enhancing lesions present at the same time), and the exclusion of other pathologies that may have similar characteristics (27).

The recent 2017 McDonald criteria (26) are used to evaluate spatial and temporal dissemination through MRI, defining more precisely the primary progressive forms. These criteria are the most used nowadays, allowing for an earlier diagnosis of MS much more than the older Poser criteria (22).

2.8. Differential diagnosis

It is very important to exclude any condition that can simulate MS in the clinical presentation and the neurological disturbance demonstrated in MRI. These main situations are (1,27):

- Acute disseminated encephalomyelitis (ADEM) and post-infectious encephalomyelitis
- Neuromyelitis optica
- Small-vessel ischemic white-matter disease and silent infarcts on brain MRI
- Stroke
- Antiphospholipid antibody syndrome
- Giant cell arteritis
- Ischemic optic neuropathies
- Vitamin B12 deficiency
- Systemic lupus erythematosus
- Behçet´s disease
- Sarcoidosis
- Tuberculomas, metastases, CNS lymphoma
- Lyme disease
- Neurosyphilis

2.9. Prognosis

The clinical evolution of MS is unpredictable, because there is a great variability between patients in their disability, some present complete remissions between relapses, while others express accumulation and progression of disability related to early, progressive, diffuse and chronic axonal damage (28). The pattern of relapses in the first years and progressive stage of the disease are the most relevant prognostic factors, patients with RRMS onset have a better evolution than those with a progressive one, and the transformation of the relapsing-remitting form to a secondary progressive form is also an indicator of the worsening of evolution (29).

The early age at onset with monosymptomatic relapsing pattern such as optic neuritis, full recovery after relapse, lower number of relapses during the first years and a prolonged time interval between the first two relapses are related with a slower course of the disease and consequently with a good prognosis (29). On the contrary, being a man, motor and brainstem involvement in the severe relapses and high activity in MRI and CSF are associated with a worse progression of the disease (30). However, the individual clinical evolution is still very unpredictable since interindividual heterogeneity is clearly wide (29). MS patients usually survive around 30 years from the onset of the disease, and their life expectancy is reduced in 5 - 10 years (31).

2.10. Treatment

MS has no cure (15), available treatments aim to reduce disease activity, prevent the appearance of new lesions in the brain MRI, accelerate recovery after attacks and delay the progression of the disease in patients with relapses (32). MS requires a multi-disciplinary assessment that involves professionals from urology, psychiatry and psychology, general practitioner, MS nursing, rehabilitation and physiotherapy, therefore it is not the exclusive job of neurologists (33).

2.10.1. Pharmacological treatment

2.10.1.1. Treatment of acute relapses

- **Methylprednisolone:** it is not yet ununderstood how Methylprednisolone has beneficial and rapid action in MS patients, especially in improving symptoms in acute relapses and shortening the time required to full recovery after exacerbation. However, in more than 40% of cases, residual damage may remain after relapse (34). Its most important side effects are severe allergy, gastrointestinal haemorrhage, hepatotoxicity, myopathy, osteonecrosis, psychosis and seizure among others (35).
- **Plasma exchange**: effective and relatively safe treatment for severe relapses that do not respond to corticosteroids at high doses, its few adverse effects are anaemia, fever, hypoalbuminemia and arterial hypotension (36).

2.10.1.2. Disease Modifying Drugs

Disease-modifying drugs (DMD) are the gold standard for the treatment of MS patients, they can reduce the frequency and intensity of relapses and the symptoms that MS causes by inhibiting the inflammatory process, as a result, progression slow down and disabilities experienced by the patient is reduced (15). Its mechanisms of action are different, as well as administration routes, approved indications and other features that can influence its use (31).

- **Interferon beta:** It is a cytokine with antiviral and immunomodulatory actions that under normal conditions is produced by the body during viral infections, it is used intramuscularly and subcutaneously (32). The main side effects are influenza-like symptoms, hepatotoxicity, inflammatory reactions at the injection site, depression, anaemia and thrombocytopenia. Usually it is well tolerated, but monitoring of complete blood count and liver function should be done. It is recommended as the first-line treatment especially to reduce relapses (by 1/3) and in case of RRMS patients with intolerance to glatiramer (21).
- **Glatiramer Acetate:** Consists of polypeptide mixture that is composed of 4 different amino acids, designed to mimic and compete with the myelin basic protein (32). It is administered subcutaneously and is effective in the treatment of RRMS reducing the rate of attacks by one

third, also it is useful in the treatment of patients with intolerance to Interferon beta**.** It is well tolerated and not associated with influenza-like symptoms. The main side effects include inflammatory reactions at the injection site, flushing, pressure on the chest, palpitations, dyspnea and anxiety (21).

- **Teriflunomide:** once-daily oral immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) blocking proliferation and reducing the number of activated B and T lymphocytes and accordingly reduces their passage through the blood brain barrier avoiding CNS damage. It is useful for patients with relapsing course of MS and worsening in the disease activity as well as for patients with a MS clinical first episode of (37).
- **Dimethyl fumarate:** it activates the Nrf2 pathway which is used to defend against inflammation and oxidative stress. Dimethyl fumarate reduces the inflammatory response and then the clinical and MRI activity of the disease (38). It has a beneficial effect in the treatment of relapsing MS, progression of disability and MRI changes. Administered orally, its main adverse effects are flushing, nausea, abdominal pain, and diarrhea (39).
- **Fingolimod:** it is a sphingosine-1-phosphate receptor modulator that causes a lymphocytes blockage in the lymph nodes, with a lower CNS migration and invasion of autoreactive lymphocytes and then inflammatory attack. Fingolimod is effective in reducing relapses and delaying the disability progression in relapsing MS patients. It can affect the liver function, causes headache, influenza infections, cough and diarrhea (32).
- **Natalizumab:** it is a selective inhibitor of adhesion molecules that binds to alpha-4-beta-1 and alpha-4-beta-7 subunit of human integrins, expressed on the surface of all leukocytes except for neutrophils. By binding to integrins, it prevents the adhesion of the alpha-4 mediated of leukocytes to their receptors. Natalizumab can increase the risk of developing a viral infection of the brain called "progressive multifocal leukoencephalopathy (PML)" in the John Cunningham Virus (JCV) carriers. It is very effective to reduce the rate of attack in MS patients and is administrated intravenously once a month (32).
- **Alemtuzumab:** it is humanized monoclonal antibody against CD52 cell surface glycoprotein with neuroprotective effects through the elimination and regulation of lymphocytes. Alemtuzumab can decrease significantly the relapse rate and disability accumulation in patients with RRMS compared to interferon beta. It is used intravenously, and its most frequent adverse effects include reactions at the infusion site, respiratory and urinary infections, thyroid diseases and impaired coagulation (32).

- **Mitoxantrone:** it is anthracenedione antineoplastic agent that reduces the progression of the EDSS and MS activity in the MRI. The most frequent side effects of mitoxantrone are cardiotoxicity, alopecia, nausea and its association to leukemia, it is recommended only for severe and advanced forms of the disease (21).

2.10.2. Non-pharmacological treatment

Its main objective is to preserve the physical, mental and social functions of the patient and consequently improve his quality of life (QoL) by reducing the disease impact on his daily life activities (DLA), making him more independent and autonomous (40). The most relevant are:

2.10.2.1. Physical therapy

Physical exercise can be useful to treat symptoms, restore function, promote well-being, optimize QoL, and increase participation in DLA (41). There is sufficient evidence on the safety and benefits of exercise therapy for patients with MS and low or moderate disability although there is little knowledge about these benefits over the long term. It includes endurance and resistance training, aerobic capacity, muscle mass, muscle strength, fatigue and depression exercises among others (40).

2.10.2.2. Vestibular rehabilitation through virtual reality

The purpose of Vestibular rehabilitation (VR) program is to promote vestibular stimulation and cerebral compensation improving the symptoms of imbalance and dizziness associated with peripheral vestibular pathology with a best functional capacity and QoL of MS patients with vestibular disorders (42). A computer technology is used to allow the patient to interact and immerse in virtual environment like in a real life, the motor learning is based on repetition, sensory feedback and patient motivation. The main used systems are virtual reality video games (Nintendo Wii, Xbox Kinect, PlayStation...) Mandala Gesture Xtreme and Haptic systems among others (43).

2.10.2.3. Occupational therapy

The aim of the occupational therapy is to improve the patient daily life and well-being, adapt environments and occupations, teach MS patient how to compensate for his deficiencies and design strategies that he can carry out to be autonomous in his DLA. The main objective for MS patients is the ability to achieve their occupations easily being satisfied and Independent (44).

2.10.2.4. Cognitive behavioural therapy

Depression is frequent among patients with MS, the worsening in disability and health-related quality of life (HRQoL) of them may be related to inadequate management of depression. Cognitive behavioural therapy (CBT) is a psychological therapy used for MS patients to alleviate depressive symptoms although there is no strong evidence about its benefits. The most commonly used types of CBT are face-to-face, group, internet and telephone-based CBT (45).

3. JUSTIFICATION

MS is a chronic inflammatory disease of the CNS characterized by the neurodegeneration and considered among the most common causes of neurological disability in young people with a remarkable increase in prevalence and incidence during past years especially in women. MS can manifest in different degrees of severity, from a few attacks to a progressive and high disability which generates a significant impact on the patients QoL and their caregivers (31), in addition, patients, families and society suffer from a very high psychosocial and substantial economic burden due to the very high cost of this chronic disease (14), because the use of health resources is greatly increased in patients with MS, and the patient labor productivity is continuously reduced, this represents a very important economic burden for the health system and for society as a whole (3). In consequence, there is an indispensable need to look for solutions to cope with the progression and activity of this disabling disease. One of the biggest challenges in the diagnosis of MS is that generally affects young people, men and especially women who are in the prime of their life and in the most productive and active life period in the vast majority of them (13).

Balance deficit is one of the initial and common disabling symptoms reported in MS patients with low level of disability. This incapacitating deficit contributes significantly to the reduction of the patient mobility, independence and the simple development of DLA, as well as it can lead to falls, indeed about 70% of MS patients fall frequently, and more than 10% of these falls produce injuries, MS patients are 3 times more likely to suffer fractures than healthy population, this causes a reduction in patient activity and decreased participation in physical activity that negatively affects the QoL experienced by the patient and their caregivers (46,47,48). Additionally, vertigo can be the first symptom of MS in approximately 5% of patients, and almost half of them suffer from vertigo years before they are definitively diagnosed with MS. Most patients present other symptoms from the brainstem or cerebellum in parallel with vertigo such as diplopia and dysarthria (49).

Rehabilitation programs aimed at improving balance and physical activity of the patient and decreasing fall risk can delay the physical and psychological impairment of the MS patient by using effective strategies in physical rehabilitation. Nevertheless, there is no strong evidence for deciding optimal mobility therapy and none for managing falls in patients with progressive MS (48).

Physical therapy is a safe and powerful non-pharmacological intervention used in patients diagnosed with MS, it has many benefits on the brain and functional capacity even though in some patients it may cause a transient aggravation of symptoms. Physical exercises aim to restore the patient's health status and prevent further deterioration by following an individualized protocol that considers the patient's medical capacity and his limitations. Therapists determine the type, intensity, frequency and duration of exercises that the patient should comply, these exercises can be

resistance or endurance training with a wide spectrum between them (50).

Several studies have evaluated the effectiveness of rehabilitative interventions through physiotherapy and concluded that they are beneficial for patients diagnosed with MS, and that can help to improve the patient disability and motor impairments (42,51) by improving postural balance, walking speed, and the ankle musculature control (52).

In clinical practice, physiotherapy is commonly used in almost all specialized medical centers to rehabilitate patients with neurological disorders such as MS, although it depends mainly on the patient's physical condition and his limitations.

Recently, numerous devices and platforms based on virtual reality have been introduced to take advantage of the great opportunities that this technology provides as one of the most relevant novelties in the physical and psychological rehabilitation of neurological diseases in general and MS in particular. Virtual reality is a simulation of the real environment generated by computer and where the patient can interact with certain elements within the simulated scenario through a human-machine interface, as a result, therapy sessions are more motivating, enjoyable and safe, and patients are more adherent to their rehabilitation. Some virtual reality systems allow patients to receive sensory and tactile feedback in real time that is very useful for motor learning, and it is possible to control each session with high precision and repetition, adapting levels of difficulty and interfaces to the needs of the patient. In addition, thanks to the new tele-rehabilitation platforms, patients can perform their VR exercises in their homes, with remote supervision by the healthcare professional (53). VR based on virtual reality aims to improve balance impairment by stimulation of the vestibular system and central compensation. Several studies carried out recently have demonstrated that virtual reality exercises are effective and have positive effects in improving balance in MS patients (42).

According to our research, only a few trials have studied the effects of VR based on cave automatic virtual environment (CAVE) to improve balance in the MS population. In addition, these trials have had several limitations, and it is difficult to draw significant conclusions about the efficacy of these therapy programs, and consequently, extrapolate the results to other populations.

Our project aims to demonstrate that VR through CAVE is an effective alternative to traditional physical therapy, able to improve balance and results in significant decrease of the risk of falls in patients diagnosed with MS and suffering from balance impairment, and consequently improve their QoL and their caregivers. For all these reasons, we need a new and strong conclusive scientific evidence to recommend and extend the use of VR through CAVE among MS patients with balance impairment in all health centers.

4. HYPOTHESES

4.1. Main hypothesis

- VR through CAVE is more effective in improving **balance** in patients with RRMS compared to traditional physical therapy.

4.2. Secondary hypotheses

- VR through CAVE is more effective than traditional physical therapy in improving the **fall risk and gait** in patients with MS.

- VR through CAVE is more effective in improving the **HRQoL** of patients with MS compared to traditional physical therapy.

- VR through CAVE is more effective in improving the **QoL of MS caregivers** compared to traditional physical therapy.

- VR through CAVE is more effective than traditional physical therapy in improving the **progression of disability** in patients with MS.

- VR through CAVE is more **cost-effective** than traditional physical therapy in improving balance in patients with MS.

5. OBJECTIVES

5.1. Main objective

The primary objective of the present study is to evaluate the effects of VR program based on CAVE on improving balance in patients with RRMS, EDSS between 3 and 5 and suffering from balance impairment and compare the effectiveness with those of a traditional physical therapy program.

5.2. Secondary objectives

- Evaluation of the effects of VR through CAVE on improving the **risk of falls and gait** compared to traditional physical therapy in patients with MS.

- Evaluation of the benefit of VR through CAVE compared to traditional physical therapy on **HRQoL** of patients with MS.

- Demonstration that VR through CAVE is more effective than traditional physical therapy in improving the **QoL of MS caregivers**.

- Assessment of the effect of VR through CAVE on the reduction of **disability progression** compared to traditional physical therapy in patients with MS.

- Comparison of the **cost effectiveness** of the two therapies.

6. METHODS

6.1. Study design

Our research team intends to conduct a multicenter randomized controlled trial, it is not possible to apply double-blind for either the patient or the researcher, because both must know the intervention before in order to carry out it. The reference center of our study will be Hospital de Figueres (HF), but we will need the collaboration and coordination with Hospital Universitari de Girona Dr Josep Trueta (HUGDJT) and Hospital Germans Trias i Pujol (HGTP) in order to achieve the required sample.

6.2. Randomization procedures

Once the inclusion and exclusion criteria have been met, selected patients will be randomly assigned in one of 2 equal groups. The sampling method will be the same and all therapists will receive a training course about the performance of each therapy in the assigned hospital in order to homogenize procedures. To minimize the observer bias to the maximum, outcome measurements during and after the trial will be assessed by an experienced researcher uninvolved in the performance of any of the two therapies. In addition, we will perform repeated measurements to increase the reliability of results. During the trial, any patient who withdraws will not be replaced.

6.3. Participants

The population of study will include patients of both sexes between 18 and 50 years old diagnosed with RRMS and who suffer from balance impairment according to the **Berg Balance Scale** (BBS). Only patients who meet all inclusion and exclusion criteria will be admitted. The diagnosis must be performed by a neurologist with a large experience in the diagnosis and treatment of MS.

6.4. Inclusion criteria

- Age between 18 and 50 years old.

- Patients must have both clinically and radiologically a confirmed diagnosis of RRMS according to the McDonald criteria.
- Patients must have a total score below 45 on the BBS.
- Patients must have an **Expanded Disability Status Scale** (EDSS) score ranging from 3 to 5
- Patients who sign the written informed consent.

6.5. Exclusion criteria

- Institutionalized patients at the time of recruitment.
- Personal history of severe psychiatric, metabolic, lung, kidney or cardiovascular diseases.
- orthopedic or joint disorders that limit range of motion.
- Patients suffering from blurred vision.
- Contraindications for rehabilitation or stability exercises.
- Pregnant women, breastfeeding or with the intention of doing so during the trial period.
- Patients with relapse within 3 months or change in MS medical treatment during last year.
- Participation in a vestibular or physical exercise program within 3 months prior to the study.
- Patients with moderate to high alcohol consumption (54).

6.6. Withdrawal criteria

- Revocation of the informed consent.
- Occurrence of complications or adverse effects related to the assigned therapy.
- Change in the treatment of MS during the trial.
- Relapse during the intervention period.
- Patients who do not comply with the trial protocol once admitted (patients who do not attend the therapy sessions or do not finish the time of exercises for 3 or more times).

Patients who withdraw from the trial will be counted in the statistical analysis but not replaced.

6.7. Sample size

In our study, we have used the GRANMO software to define the sample size. Accepting an Alfa risk of 0.05 and a Beta risk of 0.2, and in a two-sided test, we have found that 103 patients in the first group and 103 in the second group will be needed to detect at least 20% difference in balance improvement between the two interventions as statistically significant, assuming there will be a 10% follow-up loss.

6.8. Variables

6.8.1. Independent

The independent variable will be the therapeutic intervention performed by the therapist: one group will receive VR through CAVE and the other group will receive traditional physical therapy. It will be considered as a dichotomous qualitative variable.

6.8.2. Dependent

6.8.2.1. Main variable

The main dependent variable in our study will be the balance, for this reason we will use the **BBS (Annex 1. Berg Balance Scale)** to assess the balance change in each participant at the beginning, during and at the end of the intervention programs. The BBS evaluates 14 items and the total scores can range from 0 (severely affected balance) to 56 (excellent balance). In this scale, it is considered that there is a significant change in balance if at least there is a change of 8 points in the BBS between the two assessments.

All patients will be categorized into 2 groups: patients with improvement of 8 points or more on the BBS, and patients with improvement below 8 points on the BBS. It will be considered as a dichotomous qualitative variable (improvement/ no improvement in balance).

6.8.2.2. Secondary variables

The secondary dependent variables in our study are:

- **Risk of accidental falls:**

It will be evaluated by using the **Test get up and go** (TGUG) **(Annex 2. Test get up and go)**, validated to determine the risk of falls by calculating the time that the patient takes to get up from a chair, walk and return to his chair. The score interpretation is as follow:

- < 20 seconds: normal (no risk of falls).
- > 20 seconds: high risk of falls.

This is a dichotomous qualitative variable (presence or absence of accidental falls risk).

- **Gait:**

It will be assessed using the **Two Minute Walk Test** (2MWT) **(Annex 3. Two-Minute Walk Test)** which is an endurance measurement that evaluates walking distance for two minutes without assistance. The minimal detectable change (MDC) in the walking distance is 19 meters, a distance equal or greater than 19 is considered as improvement of the gait while a value less than 19 is considered non-significant.

It is a dichotomous qualitative variable (presence or absence of gait improvement).

- **HRQoL of the patient:**

HRQoL will be evaluated using the specific **Short Form-36 Questionnaire** (**SF-36).** **(Annex 4. SF-36 Questionnaire)**, it is a generic HRQoL measurement instrument with 36 questions designed to provide a profile of the health status and is applicable to both patients and healthy population. The questionnaire covers 8 dimensions, which represent the concepts of health used more frequently when HRQoL is measured, as well as other aspects related to the disease and its treatment. The evaluated dimensions are: physical functioning, physical role, corporal pain, general health, vitality, social functioning, emotional role and mental health of the patient. Additionally, the SF-36 includes a transition question about change in general health status compared to the previous year. This item is not used for the calculation of any of the 8 main dimensions. The scores of the 8 dimensions of SF-36 are ordered so that a higher value indicates better HRQoL.

For each dimension, items are coded, aggregated and transformed into a scale with a range from 0 (the worst state of health) to 100 (the best state of health). In addition, the questionnaire allows the calculation of two summary scores: physical and mental (a score of 50 each) by means of the scores weighted sum of the 8 main dimensions. To simplify interpretation, and according to Ware, Nelson, y cols (55), we are going to use the following classification:

85 – 100	Excellent
62 – 84	Very good
26 – 61	Good
1 - 25	Mild
0	Bad

It is an ordinal qualitative variable.

- **Caregiver QoL:**

The prolonged care of a dependent patient with MS concludes affecting in many cases the QoL of his caregiver. We will use the **Zarit Burden Interview (ZBI)** **(Annex 5. Zarit Burden Interview)** to evaluate the caregiver QoL. It is a popular caregiver self-report measure that contains 22 items, each item is a statement which caregiver has to answer using a 5-point scale. Response options can range from 0 (Never) to 4 (Nearly Always).

Interpretation of scores is as follow:

61 – 88	Severe burden
41 – 60	Moderate to severe burden
21 – 40	Mild to moderate burden
0 - 21	Little or no burden

It is an ordinal qualitative variable.

- **Progression of disability:**

The progression of disability will be evaluated using the **EDSS** score **(Annex 6. Expanded Disability Status Scale)** which is determined by neurological exams, it is the most widely used to assess the

functional status of patients with MS evaluating their disability. The assessment ranges from 0 (normal state of health) to 10 (death by MS). Although based on the ability of the patient to walk, it also measures the involvement of 8 functional systems: pyramidal, mental, cerebellar, brainstem, sensory, visual, intestinal and bladder functions.

It is considered that there is a sustained progression of disability if there is an increase of more than **1 point** on the EDSS score maintained for 3 months. It will be measured as a dichotomous qualitative variable (presence or absence of disability progression).

- **Cost effectiveness:**

It will be evaluated by comparing the 2 therapies in terms of resource consumption and overall costs (direct and indirect) related to each intervention. We will measure the quality-adjusted life years (QALY) gained by applying these interventions and it will be considered as a quantitative variable.

6.8.3. Covariates

- *Age*: it is measured in years and it is considered as a discrete quantitative variable.
- *Gender*: male or female, it is a dichotomous qualitative variable.
- *Concomitant treatment with other oral drugs*: it is a dichotomous qualitative variable (Yes/No)
- *Duration of MS*: each patient has a different evolution time, which can reflect the severity of MS symptoms including balance disorder. It is measured in years and it is considered as a discrete quantitative variable.
- *Number of relapses in the last 2 years*: it has an important prognostic value and will indicate the evolutionary process of MS and the degree of future disability. This is considered as a quantitative variable.

6.9. Procedures

6.9.1. Recruitment

Participants will be recruited through hospital computerized database which records the clinical and demographic data of all patients followed up in our 3 hospitals with a confirmed diagnosis of RRMS. Participants will be invited to enter our study during the usual clinical examination in their MS center or by phone. A packet of information with the description of the study and even verbal information if necessary will be provided to interested participants.

6.9.2. Data collection

Under the Data Protection Act and in order to ensure the blindness, we will assign a number to each

participant once the inclusion and exclusion criteria have been met and the patient is admitted to enter the study after signing written informed consent.

The approval of the Ethics Committee of HUGDJT will be required before the beginning of the study.

6.9.2.1. Screening visit

Interested participants will come to the neurology department of the hospital to be evaluated by the main investigator, patient data and demographic details will be collected by taking a clinic history, in addition, the patient EDSS score will be measured and pregnancy test will be performed in women, all inclusion and exclusion criteria will be checked out. An information sheet **(Annex 7. Information sheet for participants)** will be provided to each participant who must sign the written informed consent **(Annex 8. Informed consent form)** in order to be accepted in our study once all criteria have been met. Admitted participants will be randomly and equally distributed into one of the 2 groups, one group will receive VR through CAVE while the other one will receive traditional physical therapy exercises.

6.9.2.2. First visit

In this visit, the main investigator will proceed to verify eligibility by review of inclusion and exclusion criteria, then the following items will be checked by the neurologist in order to define the pre-intervention values: BBS score (3 measurements will be performed and calculation of its average in order to counteract the learning effect), EDSS score, TGUG, 2MWT, SF-36, ZBI and vital signs.

6.9.2.3. Second visit

One-month after the intervention, participants will come to neurology service of the assigned hospital to be evaluated by the neurologist. Successive visits will be performed at 3, 6 and 9 months from the beginning of the intervention.

6.9.3. Intervention

The duration of the exercise in both groups will be identical, 3 sessions per week and 45 minutes per session. Participants should arrive to the assigned hospital at least 20 minutes before the beginning of the session in order to relax and prepare for training session, the time it will be taken to get dressed and wear the special equipment will not be counted in the time of training session. The research team will document all training and evaluation sessions in each hospital.

6.9.3.1. Vestibular rehabilitation group **(Annex 9. Vestibular rehabilitation through CAVE)**

In this intervention, we will use the CAVE, a novel system that contains a room in which the coordinated projectors create a realistic 3D representation on the walls, floor and ceiling, creating the illusion of being inside the virtual environment. It is a HD CAVE visualization system that includes six sides and 12 channels, four rear projection display walls, a rear projected ceiling and a solid

acrylic floor with rear projection, each surface is 9'6 x 9'6 in size and visualizes the images of two Digital Projection Titan 3D 1080p projectors. The projected images are mixed in the middle of each surface and combine a total of 1920 x 1920 pixel with about 4,500 lumens per projector as a maximum brightness. A 41 x 78 mirror per projector (four in total) is used by each of the ceiling and floor surfaces to achieve the adequate distance from the projector to the surface, 12 projectors are used (2 projectors per side) to produce the projected images in the six-sided CAVE. HD CAVE system is also a fully-immersive VR system, equipped with a device capable of measuring reactive postural control by recording body movement, additionally it includes a 5.1 surround sound audio system and allows multiple users at the same time.

The presentation of The CAVE images is done in 3D stereo and the coordination through the Intersense IS 900 VETracker processor and Head Trackers (model: 100-91003-AWHT) in order to have a dependent stereoscopic display on the user's full viewpoint. The ultrasonic tracking emitters placed in the corners of CAVE between the vertical walls and between the walls and the ceiling allow a complete tracking of the wand and head. The units of the head tracking are placed in the realD CE4 protection glasses (Model: 100103-04) that the participant wears, at the same time the wands are used to virtually navigate through the space and interact with virtual objects. One of the CAVE walls allows entry into the space because it can move aside, participants access the CAVE wearing special protection glasses (eye tracking glasses), where they interact with objects thanks to a hand-held wireless MicroTrax Wands.

Scenarios are representations of real or abstract virtual environments, which can be loaded into space in a few seconds allowing the participant to walk through the virtual representation of real or imagined space experienced in 3D.

In this project we will use the two spaces, an abstract one without dimensions and the kitchen space in a virtual house, the duration of the 2 exercises will be 45 minutes.

a- The Imagination Scenario: (25 minutes)

The Imagination environment is a soft colored, non-dimensional and abstract space, composed of five blocks of eight pastel-colored squares sit on a circular platform hanging in the space. Individuals use the wand to choose and lift blocks, put them anywhere in the space, and assemble several blocks to build structures, the blocks emit a bell sound each time they move or touch with the wand adding to the auditory experience, an identical and new block in the original site appears every time a block is moved from the platform in order to replace it, participants can also walk through the space or navigate using the joystick on the wand. In this environment, no gravity laws are applied to the blocks and participants can cross the space as if they are surrounding the colored background.

b- The Kitchen Scenario: (20 minutes)

This is a typical apartment built in the CAVE, with furniture, wall colors and images of floors that represent what can be seen in a residential home. As in the imagination environment, participants can navigate using a joystick on the wand or walk through space. In this study, the kitchen is the center of the scenario, it is equipped with typical household items virtually represented and includes 48 movable objects with the help of the wand (pots, pans, cups and food packages) allowing the interaction of the individual with these objects in this scenario, he can open the cupboard doors and turned on the faucets, with the accompaniment of the changes in image and expected sounds. Objects in the virtual kitchen express the expected physical characteristics like falling when dropped.

6.9.3.2. Traditional physical therapy group **(Annex 10. Traditional physical therapy exercises)**

A traditional physical therapy exercises program is designed to improve balance, pelvis and trunk stability, muscle length of the lower limb, strength, and movement control, it will be performed following the **Bobath approach** which is based on the brain ability to reorganize itself from peripheral sensory stimuli, making the healthy parts of the brain able to compensate for the functions that were previously performed by damaged regions of the brain, always taking into account the needs and expectations of patients, it is so a way to balance the body in terms of functionality and mobility. The final objective is to modify the abnormal movement patterns resulting from the injury and achieve a correct movement in a physiological way, improving the balance impairment and consequently a daily life and professional activities.
In this intervention, physiotherapy will comprise 45 minutes individualized training sessions, face to face with the physical therapist, these exercises will be carried out 3 times a week, monitoring the risk of falls that the patient may have during the training session. Three different types of exercises will be performed, each one will last 15 minutes with different levels of difficulty.

a- First exercise: (15 minutes)

Patient sitting on a mat with legs stretched out and hands resting on the floor:

- the patient will try to move the weight of his body towards the right side, then he has to change moving the weight towards the left side.

Patient kneeling on a mat, resting the tips of the toes:

- the patient will sit on his heels keeping the arms crossed and then lift the pelvis until it is in the initial position.

b- Second exercise: (15 minutes)

Patient placed on all fours on a mat:

- the patient will stretch one arm forward and lower it, then he has to stretch the other arm

and after he has to lower it, next he has to stretch one leg back, lower it and stretch the other one, finally he has to lift one leg while lifting the opposite arm.

c- Third exercise: (15 minutes)

The patient will try to maintain the balance kneeling on one leg and with the other leg bent with the flat foot on the ground, then standing and having a stable surface nearby to hold on in case of imbalance, the patient has to walk by placing one foot immediately in front of the other.
Next, with the feet as close as possible to each other (if necessary, patient can use a support to reach this position) and only when stability is achieved, the patient will maintain balance and release the support, from that moment the seconds in balance must be counted, and if it is possible the patient should try to reach 20 seconds.
Now the patient will try to maintain balance with his eyes closed, always with great care.
It is possible that the patient cannot reach the suggested 20 seconds, but he can always work with the objective of increasing the time in balance.

6.9.4. Follow up

Participants will be followed up by a MS experienced neurologist uninvolved in the intervention program who will perform the scales measurement and will record any complication or harmful event that the patient can have during the intervention period, especially accidental falls. All participants will be advised not to talk about their therapy with the neurologist.
All examinations will be performed in the neurology service of each hospital. The first clinical evaluation will be carried out one month after the intervention and the **participant data sheet (Annex 11. Participant data sheet)** will be completed as the patient data are collected. After this first visit post-intervention, participants will be followed up at 3, 6 and 9 months using the specific scales and questionnaires and recording the collected data in the participant data sheet.

7. STATISTICAL ANALYSIS

All collected data will be included in our database (Access 2016) as the project progresses. The statistical analysis will be performed by a statistician uninvolved in the intervention groups using the Statistical Package for Social Sciences (IBM SPSS statistics software, Version 25.0 for Windows©).

7.1. Univariate analysis

We will express the result of our variables in each group of study depending on if they are quantitative or qualitative. All qualitative variables will be expressed as percentages (proportion), for quantitative and continuous variables, we will use mean and standard deviation (SD) or median (quartiles) depending on if we can assume a normal distribution or not.

7.2. Bivariate analysis

In order to analyze our main objective, we have considered that the independent variable in our study (VR through CAVE or traditional physical therapy) is a dichotomous qualitative variable, and the association between this variable and the dependent variable (balance change) will be evaluated using Chi-square test in case of categorical parametric data or Fisher exact test for non-parametric categorical data. For parametric quantitative data, we will use the Student's t-test if the distribution is normal, otherwise a Mann-Whitney U test will be used.

A value of $p < 0.05$ with a confidence interval of 95% will be considered as a statistically significant result.

7.3. Multivariate analysis

A multivariate logistic regression analysis will be performed to test the association of our intervention (VR through CAVE or traditional physical therapy) with the main dependent variable (balance change) adjusted for the confusion variable (covariates). For continuous variables, we will use the multivariate linear regression.

8. WORK PLAN

This project will be launched only once the approval of the Ethics Committee of HUGDJT is obtained.

Main investigators: Dra. Olga Carmona and Dra. Cecile Van Eendenburg.

Collaborators: in each hospital we will need: 2 neurologists (for patient examination and measurements performance), a physiotherapist (for physical therapy) and trained nurse (for VR CAVE therapy). In addition, we will need a statistician and a data manager for the 3 hospitals.

8.1. STAGE 1: Preparation and coordination

It will be conducted by all members of the research team.

Duration: 2 months

Objectives:

- Determination of hypotheses, objectives, variables, inclusion and exclusion criteria and study design.
- Meeting to introduce the investigation team, definition of the role of each hospital, the work plan and the schedule.
- Creation of the data collection sheet and the database design.
- Research team training before the beginning of the study by receiving a course about the trial protocol in order to homogenize procedures and standardize data collection.
- Elaboration and presentation of the proposal protocol to Ethics Committee for its approval.

8.2. STAGE 2: Interventions and data collection

As in stage 1, it will be conducted by all members of the research team.

Duration: 18 months

Objectives:

- Enrollment of patients who meet the inclusion and exclusion criteria in the neurology service of the Hospital after they sign the written informed consent.
- Distribution of patients randomly and equally in one of the two study groups: VR through CAVE group or traditional physical therapy group.
- Follow-up of patients by measuring the different scales during and after the intervention period by a neurologist uninvolved in the statistical analysis. Complications or side effects that patients may have will be reported also.
- All patient clinical outcomes will be collected, filling the data collection sheet that will be saved in our database and reviewed if required.

The research team will meet one month after the intervention to evaluate the progress of the project and decide on any modification to the trial protocol, then the second meeting will take place after 3 months and the third at the end of the study.

8.3. STAGE 3: Data analysis and interpretation of results

Duration: 3 months

Objectives:

- Statistical analysis of collected data will be carried out by an experienced statistician.
- Interpretation and discussion of results and obtaining of conclusions will be performed by the investigators.

8.4. STAGE 4: Publication and dissemination of results

Duration: 2 months

Objectives:

- Presentation of results and conclusions.
- Preliminary writing of the scientific article.
- Exhibition of results in national and international congresses on MS.
- Publication of the article in neurology journals.

9. ETHICAL ASPECTS

This trial was designed according to the ethical principles for medical research involving human subjects which have their origin in the World Medical Association in the Declaration of Helsinki elaborated in 1964 and its recent reviewed version in May 2015, the Belmont Report, the

Convention of Oviedo and the ethical and methodological aspects of Good Clinical Practice (GCP) in the European Union. The trial must be approved by the Clinical Research Ethics Committee (CEIC) of the hospital prior to its beginning.

All collected data of this trial will be obtained from the hospital of Figueres and hospital of Girona Josep Trueta, both with a highly recognized reputation on the authenticity and reliability of their data, obtained according the medical research principles previously mentioned, and respecting the four principles of Bioethics.

The patients collected data will be treated according the Spanish law of data protection to preserve the patient confidentiality (Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal, and the "Royal Decret 994/1999" related to the security of automated files that contain personal data).

Patients who agree to participate in our trial will receive a packet of information with a complete description of the procedures and even verbal information if necessary, they must sign the written informed consent in order to be admitted to the study.

10. STUDY LIMITATIONS

- The sample size has been calculated for the main objective, and it is unlikely to draw feasible conclusions for the secondary objectives, for this reason, other specifically designed trials are required to study these variables.
- We can´t ensure double blinding neither for the patient nor for the investigator, because both will know the assigned intervention before its performance, to solve this problem, the statistician and the explorer neurologist will be blind and not know which group the participant belongs to.
- It is difficult to extrapolate the results of our study to all other populations because the two interventions are therapists dependent and are based on their experience and skill, however, all our therapists will receive a training course to homogenize the procedures.
- It is difficult to predict the patient's follow-up loss, we have assumed a loss of 10%, but it can be much greater due to the unpredictable evolution of the disease that can condition the treatment change or the onset of relapse during the intervention period. For this reason, and in order to keep the patient stable, we have limited the intervention period to 3 months.
- VR via CAVE is very expensive, and the patient has to move continuously to the hospital for exercise therapy. Nevertheless, with innovative low-cost VR equipment, the patient will be able to perform his exercises himself at home and in playful way in the next future.

11. FEASIBILITY

11.1. Research team

Investigators and collaborators of our study are employees of the 3 hospitals, and the research work will be carried out during their working time, thus we don´t estimate the need for an additional budget to hire them except for the therapists and trained nurses who we estimate will both work overtime to practice the intervention for participants in each group after receiving a training course to improve their work and ensure the standardisation of procedures and study protocol, therefore an extra budget is expected. Apart from that, the hiring of an experienced statistician will be required to introduce data in database and perform the statistical analysis of the collected data as well as the hiring of a data manager.

11.2. Available means

Prior to beginning of the study, some tests and checking must be performed, particularly a clinical analysis, vital signs, pregnancy tests for women, physical and neurological examinations. All material and medical devices that will be used in these tests and checking are available in the participating hospitals and are used in the routine clinical practice, so no extra budget will be required in this sense. In addition, and to perform VR therapy, we will need VR equipment (CAVE) that is not currently available at any of the 3 hospitals, for this reason, we will order 3 complete CAVE equipment from the marketing company in rental regime for 3 months, in this way we will reduce the expenses derived from the application of vestibular intervention. Nevertheless, no extra budget will be required for physical therapy because it is implemented in our hospitals for a long time as a regular non-pharmacological therapy and our therapists have a great experience in its performance. Other expected budgets will include insurance policies, publication of results, conferences and congresses and coordination meetings of the research team.

11.3. Patients recruitment

According to the neurology service data, patients diagnosed with MS who possibly meet inclusion and exclusion criteria and who are in follow-up in our 3 hospitals exceed 500 patients, estimating that about a 10% of these patients will not accept to participate in our study, and other 10% will not meet all inclusion and exclusion criteria, we calculate that we will have enough patients to launch this study. Considering that every month, approximately 25 patients with RRMS who possibly meet all criteria visit our 3 hospitals for routine check-ups, we estimate that about 9 months will be required to enroll all patients. The estimated total time of study is approximately 25 months.

12. PROJECT IMPACT AND APPLICABILITY

With this project, we like to obtain more evidence about the indication of VR through CAVE as the non-pharmacological first-line treatment of balance impairment in patients diagnosed with MS. Several trials have shown the efficacy and safety of this therapy for some neurological diseases, but only a few of them have tested this strategy in MS population and most of them have had several limitations to achieve relevant conclusions. The availability of practicing VR exercises at home and in a playful way by means of the low-cost virtual reality equipment is already possible and is expected to be expanded soon. Therapists can monitor and supervise the patient's developmental process live and online.

For the national health system, this will reduce the costs associated with moving the patient to the rehabilitation center, as well as the costs associated with the rehabilitation itself. In addition, it could be very useful in patients with disabilities or reduced mobility who are not able to carry out traditional physical therapy making the patient more motivated.

If we prove our hypothesis and draw solid conclusions, VR through CAVE will not only benefit MS patients, but could be tested in other neurological diseases making it a reference therapy to be implemented in our medical centers.

With increasing technological advances, rehabilitation of patients with neurological disorders can be significantly improved, allowing them to become more autonomous and have a better QoL.

13. BUDGET

The research team are employees of the 3 hospitals and they will not receive any compensation for their work in this trial, however we must hire a statistician to perform the statistical analysis, we estimate a budget of **1.200€** (40€ per hour, and a total of 30 hours). The therapist and trained nurse's overtime is estimated at 1 hour per patient and week, we calculate that in all the intervention, 12 hours overtime per patient will be necessary with a total cost of **74.160€** (12 hours x 206 patients x 30€ per hour). In addition, a data Manager will be required to perform the data monitoring and the quality control of the process with an estimated budget of **3.780€** (35€ per hour, estimating 3 hours per week for 36 weeks).

For our experimental intervention, CAVE equipment will be rented for 3 months, and we estimate a total cost of **4.000€** derived from the management of the equipment, transport and start up.

The printed material costs (advertisements, information sheets for participants, written informed consent, participant data sheets and invitations) are estimated in **150€**. Publication and dissemination budget is estimated in **2.300€**, conferences and congresses attendance, inscription,

travel and accommodation expenses of the research team are estimated to be around **1.400€**. Regarding the meeting and coordination expenses, an approximate budget of **450€** is expected (3 meetings and 150 € per meeting). Finally, a total cost of insurance policies is estimated in **18.540€**. The detailed total cost of this trial is explained in the following table.

CONCEPT	AMOUNT	COST/UNIT	SUBTOTAL
STAFF COST			
Statistician	30 hours	40€/h	1.200,00€
Data manager	3 h/week x 36 weeks	35€/h	3.780,00€
Therapist & nurse overtime	12 hours x 206 patients	35€/h	86.520,00€
Coordination & meetings	3	150€	450,00€
SERVICES & MATERIAL COST			
CAVE expenses	1	4.000€	4.000,00€
Printing & others	1	150€	150,00€
PUBLICATION & DISSEMINATION COST			
Publication cost	1	2.300€	2.300,00€
conferences & congresses	1	1.400€	1.400,00€
INSURANCE POLICIES COST			
Insurance policies	206	90€	18.540,00€
TOTAL STUDY COST			**118.340,00€**

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15. ANNEXES

ANNEX 1*. *Berg Balance Scale (BBS)

The Berg Balance Scale (BBS) was developed to measure balance among older people with impairment in balance function by assessing the performance of functional tasks. It is a valid instrument used for evaluation of the effectiveness of interventions and for quantitative descriptions of function in clinical practice and research. The BBS has been evaluated in several reliability studies. *A recent study of the BBS, which was completed in Finland, indicates that a change of eight (8) BBS points is required to reveal a genuine change in function between two assessments among older people who are dependent in ADL and living in residential care facilities.*

Description:
14-item scale designed to measure balance of the older adult in a clinical setting.

Equipment needed: Ruler, two standard chairs (one with arm rests, one without), footstool or step, stopwatch or wristwatch, 15 ft walkway

Completion:

Time: 15-20 minutes

Scoring: A five-point scale, ranging from 0-4. "0" indicates the lowest level of function and "4" the highest level of function. Total Score = 56

Interpretation:
41-56 = low fall risk
21-40 = medium fall risk
0 –20 = high fall risk

A change of 8 points is required to reveal a genuine change in function between 2 assessments.

Berg Balance Scale

Name: _____ Date: _____

Location: _____ Rater: _____

ITEM DESCRIPTION	SCORE (0-4)
Sitting to standing	_____
Standing unsupported	_____
Sitting unsupported	_____
Standing to sitting	_____
Transfers	_____
Standing with eyes closed	_____
Standing with feet together	_____
Reaching forward with outstretched arm	_____
Retrieving object from floor	_____
Turning to look behind	_____
Turning 360 degrees	_____
Placing alternate foot on stool	_____
Standing with one foot in front	_____
Standing on one foot	_____

Total _____

GENERAL INSTRUCTIONS

Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:

- the time or distance requirements are not met
- the subject's performance warrants supervision
- the subject touches an external support or receives assistance from the examiner

Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing is a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5, and 10 inches. Chairs used during testing should be a reasonable height. Either a step or a stool of average step height may be used for item # 12.

Berg Balance Scale

SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hand for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or stabilize
( ) 0 needs moderate or maximal assist to stand

STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding on.
( ) 4 able to stand safely for 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unsupported

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely for 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assist to sit

TRANSFERS
INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cuing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays safely
( ) 0 needs help to keep from falling

STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding on.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds

Berg Balance Scale continued…

REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently 25 cm (10 inches)
( ) 3 can reach forward 12 cm (5 inches)
( ) 2 can reach forward 5 cm (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cuing
( ) 0 needs assistance while turning

PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in > 20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete > 2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding on.
( ) 4 able to lift leg independently and hold > 10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold ≥ 3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.
( ) 0 unable to try of needs assist to prevent fall

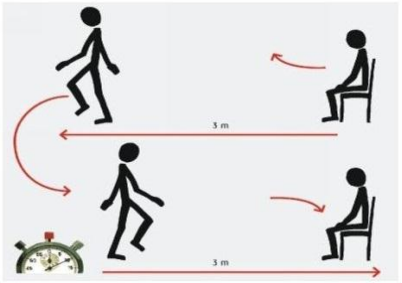
( ) TOTAL SCORE (Maximum = 56)

http://www.aahf.info/pdf/Berg_Balance_Scale.pdf

ANNEX 2. *Test get up & go (TGUG)*

Test get up and go

- The patient sits in a chair with arms
- It indicates that get up (start timing test), and walk 3 meters, turn around and sits back down in the initial chair (timing end)
- Interpretation:
  - < 20 seconds: normal
  - > 20 seconds: high risk of falls



http://airemb.es/wp-content/uploads/2016/04/airemb-seccion-reumatologia-hospital-marina-baixa-prueba-levanta-y-anda-test-get-up-and-go-espanol-english.pdf

ANNEX 3. *Two-Minute Walk Test (2MWT)*

2 Minute Walk Test Instructions

General Information:

- individual walks without assistance for 2 minutes and the distance is measured
  - start timing when the individual is instructed to "Go"
  - stop timing at 2 minutes
  - assistive devices can be used but should be kept consistent and documented from test to test
  - if physical assistance is required to walk, this should not be performed
  - a measuring wheel is helpful to determine distance walked
- should be performed at the fastest speed possible

Set-up and equipment:

- ensure the hallway free of obstacles
- stopwatch

Patient Instructions (derived from references below):

"Cover as much ground as possible over 2 minutes. Walk continuously if possible, but do not be concerned if you need to slow down or stop to rest. The goal is to feel at the end of the test that more ground could not have been covered in the 2 minutes."

Minimal Detectable Change (MDC)

Lower Extremity Amputation:
(Resnik & Borgia, 2011, LE Amputation)
MDC (calculated) = 34.3 meters or 112.5 feet (90% confidence)

Multiple Sclerosis:
(Gijbels et al, 2010, Multiple Sclerosis)
MDC = 19.21 meters (95% confidence)

Neurologic:
(Rossier & Wade, 2001, Neurologic)
MDC (calculated) = 16.4 meters or 53.8 feet (95% confidence)

Older Adults:
(Connelly & Thomas, 2009, Older Adults)
MDC (calculated) = 12.2 meters or 40 feet (90% confidence)

Stroke:
(Hiengkaew et al, 2012, Chronic Stroke)
MDC = 13.4 meters (95% confidence)
(Gijbels et al, 2011)
MDC (calculated) = 21.04 meters (95% confidence)

Normative Data
Multiple Sclerosis:
(Gijbels et al, 2010, Multiple Sclerosis)
Mean (SD) 2MWT (m) score = 144 (49), range = 92-630)
Mean (SD) 2MWT (m) score for mild MS = 173 (31), range = 108-220
Mean (SD) 2MWT (m) score for moderate MS = 104 (41), range = 40-172)
(Gijbels et al, 2012, n = 189, mean age = 47 (11) years, European and US sample, cross-sectional multicentre design, Multiple Sclerosis)
Mean (SD) gait velocities (m/s) – static start, fastest speed; 1.14 (0.42), range = 0.31 to 2.00
Mild MS (EDSS < 4.0, n = 99) Mean (SD) gait velocities (m/s); 1.39 (0.31), range = 0.58 to 2.00
Moderate MS (EDSS 4.5-6.5, n = 79) Mean (SD) gait velocities (m/s); 0.81 (0.30), range=0.31 to 1.67

Older Adults:
(Connelly & Thomas, 2009, Older Adults)
Mean (SD) 2MWT for long term care group (LTC); 77.5 (25.6) meters
Mean (SD) 2MWT for retirement dwelling older adults; 150.4 (23.1) meters

SCI:
(Lemay & Nadeau, 2010; n = 32; mean age = 47.9 (12.8); mean time post lesion 77.2 (44.3) days, SCI)
Mean (SD) 2MWT (m) score; 109.3 (48.6), range = 11 to 214
Mean (SD) 2MWT for Paraplegia; 101.3 (50.0), range = 11 to 212
Mean (SD) 2MWT for Tetraplegia; 115.9 (48.0), range = 43 to 214

Stroke:
(Gijbels et al, 2011, Chronic Stroke)
Mean (SD) 2MWT; 149 (48), range = 30 to 223 meters

147

2 Minute Walk Test

Name:_____

Assistive Device and/or Bracing Used:_____

Date:_____

Distance ambulated in 2 minutes: _____

Date:_____

Distance ambulated in 2 minutes: _____

Date:_____

Distance ambulated in 2 minutes: _____

Date:_____

Distance ambulated in 2 minutes: _____

ANNEX 4. *Short Form-36 Questionnaire (SF-36)*

11549035

Datos para el estudio

Día:	Mes:	Año: (20...)	Número identificador:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ Enero ☐ Julio	0 ☐ ☐	0 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10	☐ Febrero ☐ Agosto	1 ☐ ☐	1 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15	☐ Marzo ☐ Septiembre	2 ☐ ☐	2 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ 16 ☐ 17 ☐ 18 ☐ 19 ☐ 20	☐ Abril ☐ Octubre	3 ☐ ☐	3 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ 21 ☐ 22 ☐ 23 ☐ 24 ☐ 25	☐ Mayo ☐ Noviembre	4 ☐ ☐	4 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ 26 ☐ 27 ☐ 28 ☐ 29 ☐ 30	☐ Junio ☐ Diciembre	5 ☐ ☐	5 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ 31		6 ☐ ☐	6 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		7 ☐ ☐	7 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		8 ☐ ☐	8 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		9 ☐ ☐	9 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Cuestionario de Salud SF-36 (versión 2)

Versión española de SF-36v2™ Health Survey © 1996, 2000
adaptada por J. Alonso y cols 2003.

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d'Investigació Mèdica. IMIM

Este instrumento ha superado los estándares de calidad del **Medical Outcome Trust** y de la Red Cooperativa para la Investigación en Resultados de Salud y Servicios Sanitarios (**Red IRYSS**).
El cuestionario y su material de soporte están disponibles en BiblioPRO, la biblioteca virtual de la Red IRYSS (www.rediryss.net).

Su Salud y Bienestar

Por favor conteste las siguientes preguntas. Algunas preguntas pueden parecerse a otras pero cada una es diferente.

Tómese el tiempo necesario para leer cada pregunta, y marque con una ☒ la casilla que mejor describa su respuesta.

¡Gracias por contestar a estas preguntas!

1. En general, usted diría que su salud es:

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Excelente	Muy buena	Buena	Regular	Mala

2. ¿Cómo diría usted que es su salud actual, comparada con la de hace un año?:

Mucho mejor ahora que hace un año	Algo mejor ahora que hace un año	Más o menos igual que hace un año	Algo peor ahora que hace un año	Mucho peor ahora que hace un año
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 v2.0

3. Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer en un día normal. Su salud actual, ¿le limita para hacer esas actividades o cosas? Si es así, ¿cuánto?

	Sí, me limita mucho	Sí, me limita un poco	No, no me limita nada
a Esfuerzos intensos, tales como correr, levantar objetos pesados, o participar en deportes agotadores.	☐ 1	☐ 2	☐ 3
b Esfuerzos moderados, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de 1 hora.	☐ 1	☐ 2	☐ 3
c Coger o llevar la bolsa de la compra.	☐ 1	☐ 2	☐ 3
d Subir varios pisos por la escalera.	☐ 1	☐ 2	☐ 3
e Subir un sólo piso por la escalera.	☐ 1	☐ 2	☐ 3
f Agacharse o arrodillarse.	☐ 1	☐ 2	☐ 3
g Caminar un kilómetro o más	☐ 1	☐ 2	☐ 3
h Caminar varios centenares de metros.	☐ 1	☐ 2	☐ 3
i Caminar unos 100 metros.	☐ 1	☐ 2	☐ 3
j Bañarse o vestirse por sí mismo.	☐ 1	☐ 2	☐ 3

4. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de su salud física?

	Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
a ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b ¿Hizo menos de lo que hubiera querido hacer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c ¿Tuvo que dejar de hacer algunas tareas en su trabajo o en sus actividades cotidianas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d ¿Tuvo dificultad para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 v2.0

5. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido o nervioso)?

	Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
a ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas por algún problema emocional?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b ¿Hizo menos de lo que hubiera querido hacer por algún problema emocional?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c ¿Hizo su trabajo o sus actividades cotidianas menos cuidadosamente que de costumbre, por algún problema emocional?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. Durante las 4 últimas semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas?

Nada	Un poco	Regular	Bastante	Mucho
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. ¿Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas?

No, ninguno	Sí, muy poco	Sí, un poco	Sí, moderado	Sí, mucho	Sí, muchísimo
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?

Nada	Un poco	Regular	Bastante	Mucho
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 v2.0

9. Las preguntas que siguen se refieren a cómo se ha sentido y cómo le han ido las cosas durante las 4 últimas semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted. Durante las últimas 4 semanas ¿con qué frecuencia...

	Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
a se sintió lleno de vitalidad?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b estuvo muy nervioso?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c se sintió tan bajo de moral que nada podía animarle?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d se sintió calmado y tranquilo?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e tuvo mucha energía?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f se sintió desanimado y deprimido?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g se sintió agotado?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h se sintió feliz?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i se sintió cansado?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. Durante las 4 últimas semanas, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)?

Siempre	Casi siempre	Algunas veces	Sólo alguna vez	Nunca
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Por favor diga si le parece CIERTA o FALSA cada una de las siguientes frases:

	Totalmente cierta	Bastante cierta	No lo sé	Bastante falsa	Totalmente falsa
a Creo que me pongo enfermo más facilmente que otras personas	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Estoy tan sano como cualquiera	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Creo que mi salud va a empeorar	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Mi salud es excelente	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Gracias por contestar a estas preguntas

SF-36 v2.0

http://www.ser.es/wp-content/uploads/2015/03/SF36_CUESTIONARIOpdf.pdf

ANNEX 5. Zarit Burden Interview (ZBI)

The Zarit Burden Interview

0: NEVER
1: RARELY
2: SOMETIMES
3: QUITE FREQUENTLY
4: NEARLY ALWAYS

Please circle the response the best describes how you feel.

Question	Score
1 Do you feel that your relative asks for more help than he/she needs?	0 1 2 3 4
2 Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	0 1 2 3 4
3 Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0 1 2 3 4
4 Do you feel embarrassed over your relative's behaviour?	0 1 2 3 4
5 Do you feel angry when you are around your relative?	0 1 2 3 4
6 Do you feel that your relative currently affects our relationships with other family members or friends in a negative way?	0 1 2 3 4
7 Are you afraid what the future holds for your relative?	0 1 2 3 4
8 Do you feel your relative is dependent on you?	0 1 2 3 4
9 Do you feel strained when you are around your relative?	0 1 2 3 4
10 Do you feel your health has suffered because of your involvement with your relative?	0 1 2 3 4
11 Do you feel that you don't have as much privacy as you would like because of your relative?	0 1 2 3 4
12 Do you feel that your social life has suffered because you are caring for your relative?	0 1 2 3 4

Question		Score
13	Do you feel uncomfortable about having friends over because of your relative?	0 1 2 3 4
14	Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?	0 1 2 3 4
15	Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	0 1 2 3 4
16	Do you feel that you will be unable to take care of your relative much longer?	0 1 2 3 4
17	Do you feel you have lost control of your life since your relative's illness?	0 1 2 3 4
18	Do you wish you could leave the care of your relative to someone else?	0 1 2 3 4
19	Do you feel uncertain about what to do about your relative?	0 1 2 3 4
20	Do you feel you should be doing more for your relative?	0 1 2 3 4
21	Do you feel you could do a better job in caring for your relative?	0 1 2 3 4
22	Overall, how burdened do you feel in caring for your relative?	0 1 2 3 4

Interpretation of Score:

0 - 21 little or no burden
21 - 40 mild to moderate burden
41 - 60 moderate to severe burden
61 - 88 severe burden

Patient last name: . . . . . Date of birth: . . . . / . . . . / . . . . . .
Patient first name: . . . . . Date: . . . . / . . . . / . . . . . .

http://dementiapathways.ie/_filecache/edd/c3c/89-zarit_burden_interview.pdf

ANNEX 6. *Expanded Disability Status Scale (EDSS)*

- ❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

- ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

- ❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

- ❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

- ❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

- ❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

- ❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

- ❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

- ❑ 10.0 - Death due to MS.

---

*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

http://camapcanada.ca/EDSS_form_MS.pdf

ANNEX 7. Information sheet for participants

Title: "Vestibular rehabilitation through Cave Automatic Virtual Environment versus traditional physical therapy to improve balance in patients with multiple sclerosis: a multicenter randomized controlled trial."

Introduction

We are pleased to inform you about a project that will be carried out at the neurology unit of the hospital of Figueres, hospital universitari de Girona Dr. Josep Trueta and hospital Germans Trias i Pujol, on the treatment of balance impairment in patients with multiple sclerosis, to which you are invited to participate. The study has already been reviewed and approved by the Ethical Committee of the Hospital.

Please, take the time to carefully read the following information and decide whether you want to participate or not.

Purpose of the study

The aim of this study is to analyze the improvement in balance in patients diagnosed with multiple sclerosis and to compare the efficacy of two non-pharmacological therapeutic interventions already studied, the efficacy of physiotherapy and virtual rehabilitation through the cave automatic virtual environment have been demonstrated separately in several studies, but they had not been compared each other. With the results of this trial, we believe that we will be able to define which is the most suitable therapy among the 2 for each patient according to the efficacy in the improvement of balance, risk of falls and quality of life of the patient and his caregivers.

Voluntary participation & Economic compensation

If you are diagnosed with multiple sclerosis, and you meet all the inclusion and exclusion criteria, you can participate in the study. We want to clarify that your collaboration in the study is totally voluntary, you may decide not to participate or change your decision and withdraw your informed consent at any time, your decision will not condition in any way the attention you receive in the present or in the future. In the same way, participants will not be economically compensated for their participation.

General description of the study

If you agree to participate in this project, you will be subjected to a series of more specific tests that will allow us to know if you are a candidate for participation. The tests to be performed are the same as those we would apply outside the study, which would not imply additional risks. Each patient will undergo a clinical interview with physical, psychiatric and neurological examination, vital signs, clinical and immunological analysis, and pregnancy test in women.

Patients will be distributed randomly in two groups. Each group will receive a different therapy: the

first group will receive vestibular rehabilitation through Cave Automatic Virtual Environment while the second group will receive traditional physical therapy exercises, patient will be aware of the therapy he will receive from the beginning.

follow up

The follow-up will be done during and after the intervention in the assigned hospital. For the purpose of this study, a follow-up of 6 months is necessary. Each one of these visits will consist as the initial visit, on a clinical history, physical examination and filling the quality of life forms.

Risks

As in almost any study, the possibility of adverse effects or complications exists with the two therapies of our study even though it is minimal, the most important complications are the accidental falls that the participant may suffer during the training session. In case of appearance, they will be treated as necessary, always having as a priority the well-being of the patient.

Commitment of the patient to the data collection

The research team asks the participants for the commitment to complete the follow-ups and the therapy sessions and provide true information. The participating individuals are free to leave the study at any time without repercussions.

Results and benefit of participation

The results of this research will be available for patient consultation. The benefits derived from the research can benefit the participant as well as other people, and these will be properly used to achieve the objectives of the study and will serve as the basis for future research in this field.

Confidentiality of data

The research team is committed to adopt measures that ensure the confidentiality of their data in compliance with Organic Law 15/1999. Therefore, the information collected will be managed anonymously and will only be used for research purposes. The patient may exercise his right to access, modify, oppose and cancel his data at any time.

Insurance

The promoter of the study has an insurance policy that conforms to current legislation and will provide compensation in case of detriment to patient health that may occur when participating in the study.

ANNEX 8. *Informed consent form for participation in a clinical trial*

Title: "Vestibular rehabilitation through Cave Automatic Virtual Environment versus traditional physical therapy to improve balance in patients with multiple sclerosis: a multicenter randomized controlled trial."

Name and surname:

_____

Date of birth: ___ / ___ / _____ Contact phone number: _____

The person undersigning declares:

- Have read carefully the information sheet.
- Have received all the information considered timely about the study.
- Have had the opportunity to discuss this information with (Name of researcher) _____ _____, who has answered clearly to your questions.
- Understand that participation in this study is totally voluntary, and disinterested.
- Understand what is expected of him / her in the study, and be in agreement with the conditions.
- Understand that you can withdraw your consent at any time, without giving explanations, without giving justifications, and without conditioning your healthcare in the future.

For this to be true, sign this document in _____ a day _____

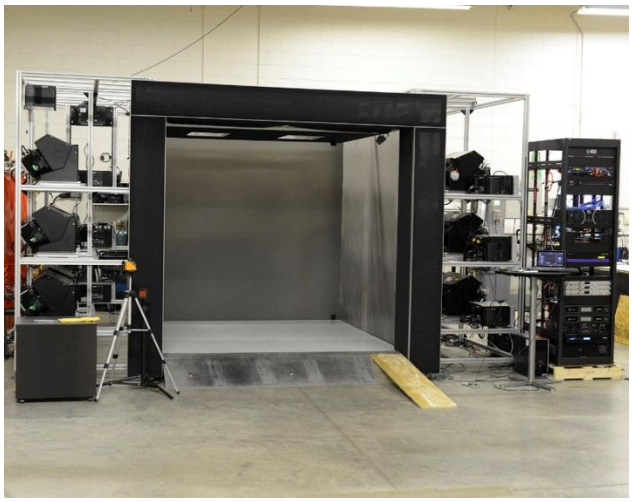
The participant	The researcher
_____	_____

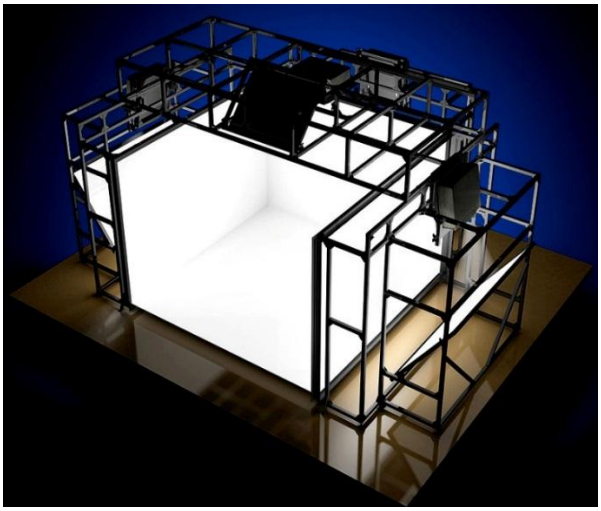
ANNEX 9. *Vestibular rehabilitation through CAVE*

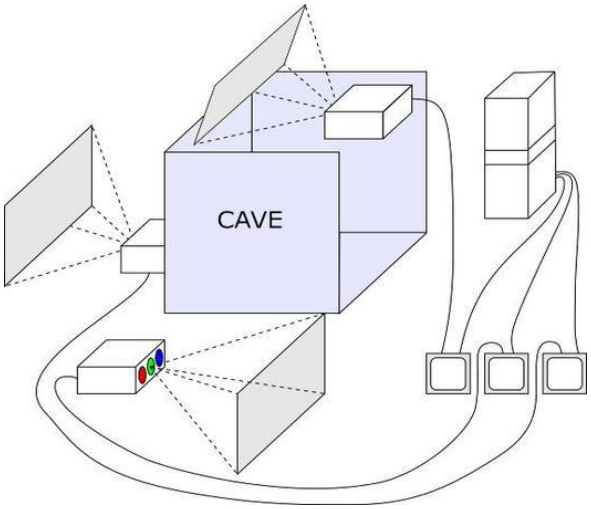
a- The Imagination Scenario

b- The kitchen Scenario

https://blogs.discovery.wisc.edu/kponto/publications/



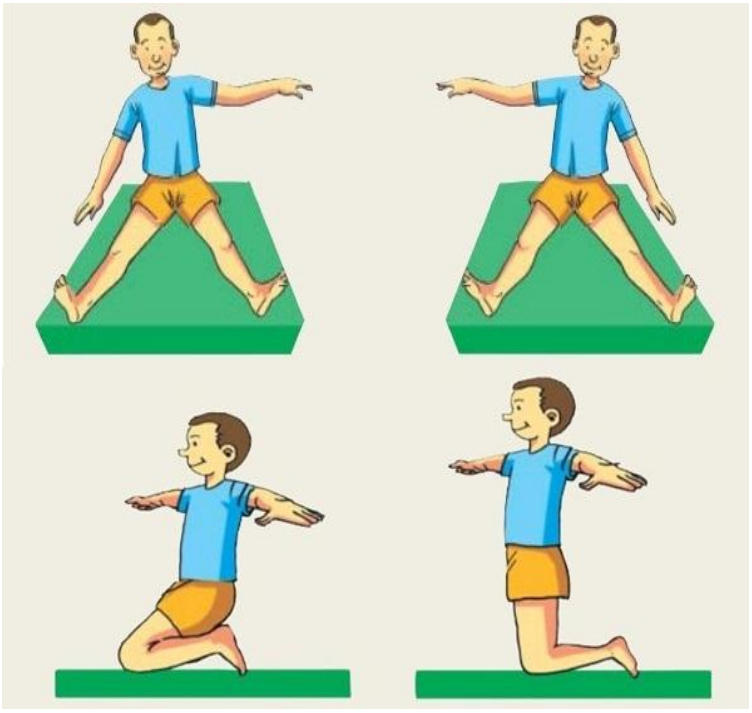




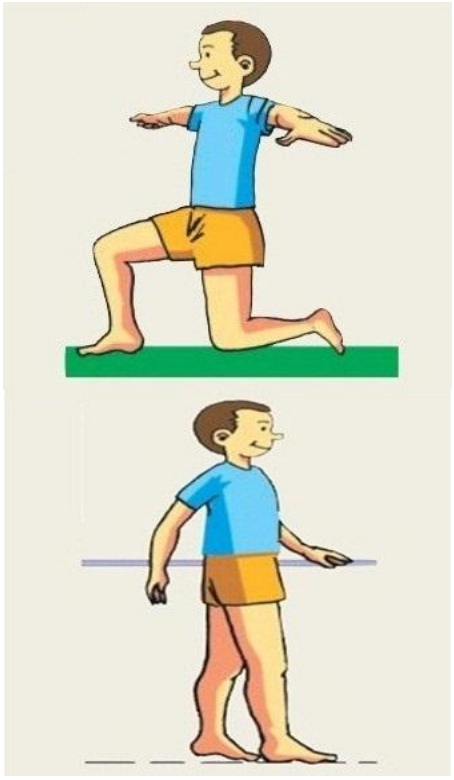
https://www.werigi.com/cave
http://www.indiana.edu/~rcapub/v21n2/p28.html
https://writingandmultimedia.wikispaces.com/The+CAVE+VR+System
https://www.roadtovr.com/smi-3d-eye-tracking-glasses/
https://www.researchgate.net/figure/Photo-of-the-Magic-Wand-first-interaction-technique-in-CAVE_261044291

ANNEX 10. Traditional physical therapy exercises

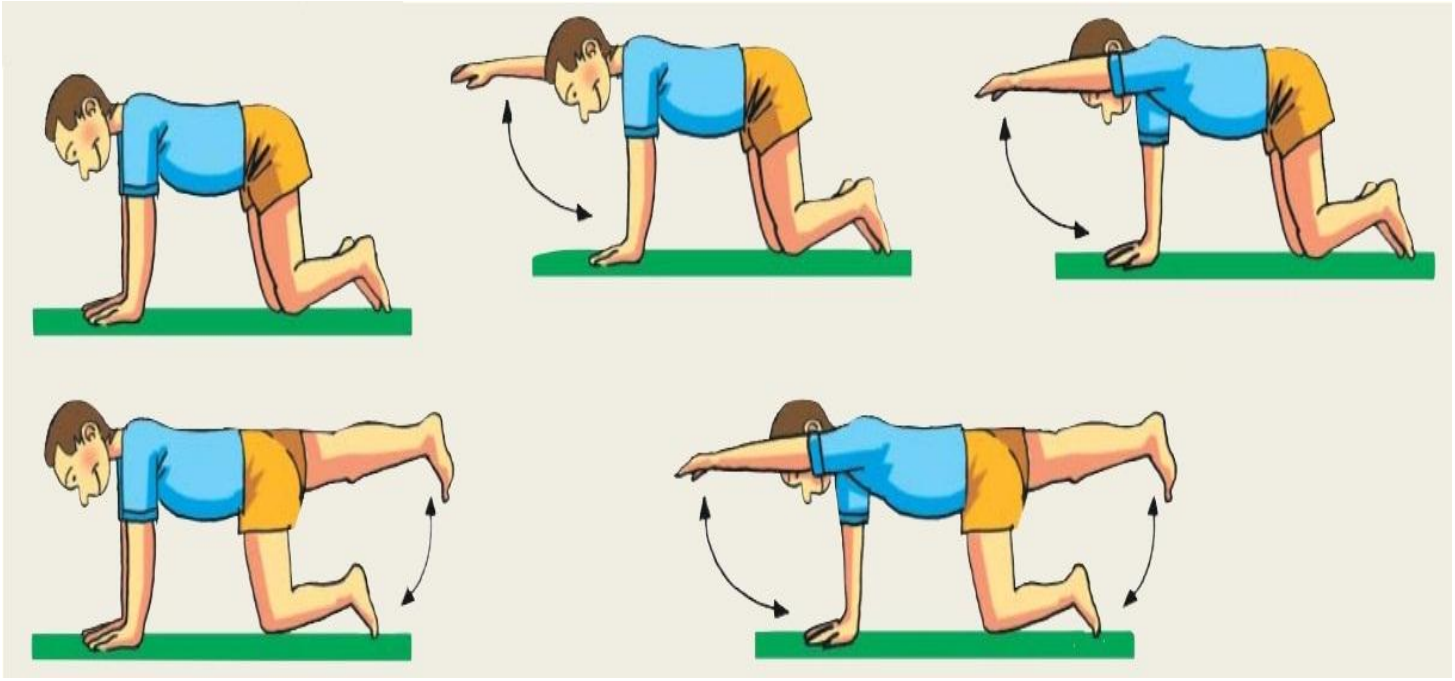
a- First exercise



c- Third exercise



b- Second exercise



https://www.fem.es/imatges/web/documents/3ejerequ.pdf

ANNEX 11. *Participant data sheet*

TITLE: ***Vestibular rehabilitation through Cave Automatic Virtual Environment versus traditional physical therapy to improve balance in patients with multiple sclerosis. A multicenter randomized controlled trial.***

PARTICIPANT DATA SHEET

Clinician must fill patient's data

NAME: _____

FIRST and SECOND SURNAME: _____

DIRECTION: _____

PROFESSION: _____

HOSPITAL: _____

TYPE OF INTERVENTION: _____

DATE:
(____/____/_____)

DATE OF BIRTH: _____

COUNTRY OF BIRTH: _____

YEAR OF IMMIGRATION: _____

TELEPHONE: _____

EMAIL: _____

SEX: MALE ▪ FEMALE ▪

PHYSICAL EXAMINATION

BMI (kg/m2): Blood pressure:
Heart rate: Breathing frequency:

CLINICAL HISTORY

ALLERGIES: _____

CHRONIC DISEASES: _____

FAMILY HISTORY: _____

REGULAR MEDICATION *(Other than for multiple sclerosis)*

Drug name	***Dosage***

Age at diagnosis of Multiple Sclerosis:

Age at symptom / sign onset:

Current EDSS:

Disease course at present (choose one):

Relapsing-remitting	
Secondary progressive (relapsing-remitting evolving into progressive)	
Progressive-relapsing (progressive with superimposed relapses)	
Primary progressive	

CURRENT FIRST-LINE MEDICATION FOR MULTIPLE SCLEROSIS

Drug name	***Dosage***
Interferon beta	
Glatiramer Acetate	
Teriflunomide	
Dimethyl fumarate	
Others	

PRE-INTERVENTION MEASUREMENTS

Scale	***Score***
Berg Balance Scale (BBS)	
Test get up and go (TGUG)	
Two-Minute Walk Test (2MWT)	
Short Form-36 (SF-36)	
Expanded Disability Status Scale (EDSS)	

FOLLOW UP

Scale	***1 Month***	***3 Months***	***6 Months***	***9 Months***
BBS				
TGUG				
2MWT				
SF-36				
EDSS				

	1 Month	***3 Months***
COMPLICATIONS REPORTED		

ANNEX 12. Chronogram

	RESEARCH TEAM	March 2018 April 2018	May 2018 October 2019	Nov 2019 Dec 2019	January 2020 January 2020	February 2020 March 2020
Preparation & coordination	All the research team					
Interventions & data collection	Investigators & collaborators					
Data analysis	Investigators & statistician					
Interpretation of results	Investigators					
Publication & dissemination	Investigators					