BMJ Open

The role of video games therapy on balance and dual tasking in multiple sclerosis. A randomized controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052005
Article Type:	Protocol
Date Submitted by the Author:	02-Apr-2021
Complete List of Authors:	Baroni, Andrea; University of Ferrara, Department of Neuroscience and Rehabilitation Fregna, Giulia; University of Ferrara, Department of Neuroscience and Rehabilitation Severini, G; School of Electrical and Electronic Engineering Zani, Giulia; University of Ferrara, Department of Neuroscience and Rehabilitation Milani, Giada; Doctoral Program in Translational Neurosciences and Neurotechnologies Basaglia, Nino; University of Ferrara, Department of Neuroscience and Rehabilitation Straudi, Sofia; Azienda Ospedaliero Universitaria di Ferrara Arcispedale Sant'Anna, Department of Neuroscience and Rehabilitation
Keywords:	Multiple sclerosis < NEUROLOGY, REHABILITATION MEDICINE, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The role of video games therapy on balance and dual tasking in multiple sclerosis. A randomized controlled trial.

Andrea Baroni[1], PhD, Giulia Fregna[1], MS, Giacomo Severini[2], PhD, Giulia Zani[1], MS, Giada Milani[3], MS, Nino Basaglia[1], MD, Sofia Straudi[1], MD, PhD

Affiliations:

[1]Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy

[2] School of Electrical and Electronic Engineering, University College Dublin, Dublin, Ireland

[3] Ferrara University, Doctoral Program in Translational Neurosciences and Neurotechnologies, Ferrara, Italy

Correspondence

Dr. Sofia Straudi, MD, PhD. Neuroscience and Rehabilitation Department, Ferrara University Hospital. Via Aldo Moro 8, 44124 Cona, Ferrara, Italy. 0039 0532236953

ABSTRACT

Introduction Multiple Sclerosis is one of the major causes of disability in young adults and influence balance, with poor outcome on daily living activities and participation in social life. Cognitive domain is frequently impaired in people with MS (PwMS), with particular regard to capacity to perform dual-task activities. Impaired cognitive processing abilities need to be treated and motor and cognitive aspects does not have to be considered separately. Recently, video-game therapy (VGT) has been used in rehabilitation to improve motor outcomes and cognitive processing speed. The aim of this study is to test efficacy of commercially available VGT on balance and dual tasking in PwMS compared to a standardized balance platform training (BPT).

Methods and analysis This will be a parallel-assignment, double-blinded randomized control trial. Forty-eight (24 per arm) PwMS (EDSS 4-5.5) will be randomly assigned to receive 1-h training session over 4 weeks (three sessions/week) of either: (1) VGT on commercial video game console to train balance and mobility related activities or (2) BPT to perform balance, postural stability and weight-shifting exercises with and without visual feedback. The same assessor will evaluate outcome measures at three time points: before and after the twelve training sessions and at three months follow-up. The primary outcome is balance, assessed by Timed Up and Go (TUG) test. We will also assess gait, risk of fall, fatigue and health related quality of life as well as cognitive and psychological aspects (depression, anxiety and attentional performance) and stability through posturographic evaluation. Dual-tasking assessment will be performed combining posturographic and neuropsychological tests. Data analysis will be performed to compare efficacy of the two treatments.

Ethics and dissemination Ethical approval has been granted from local Ethics Committee. Study results will be communicated through high-quality journals and national and international conferences.

Trial registration ClinicalTrials.gov, Identifier: NCT03353974

Keywords Multiple sclerosis, video-game, balance, dual-task

Strengths and limitations of this study

- This will be the first trial to establish efficacy of video-game therapy on dual-tasking ability.
- This trial will use objective evaluation as posturographic assessment to test balance.
- This trial is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.
- Results from this trial will need a larger sample to be confirmed.

INTRODUCTION

Multiple Sclerosis (MS) is characterized by the presence of multifocal inflammatory demyelinated plaques distributed over time and space within Central Nervous System (CNS). It affects approximately 1.3 million people worldwide and is a major cause of chronic neurological disability in young adults aged 18–50 years.[1,2]

Deficits in balance control and cognition are prevalent impairments in people with MS (PwMS),[3] even at early stage and in absence of clinical disability.[4] Previous studies have reported that 30 to 63% of PwMS experience a fall event between 1 and 12 months since the onset of the disease.[5] Balance maintenance is a complex task that depends on the continuous flow of proprioceptive information from the muscles, tendons, joints, skin, vestibular and visual systems toward the CNS.[6] In PwMS, the extended damage caused in the CNS leads to a decreased ability in integrating the afferent proprioceptive information, thus negatively influencing postural response and the capability to maintain balance safely.[5,7] Balance impairment can consistently limit the activities of daily living and the active participation in social life.

Cognitive impairment is various among PwMS with current prevalence rates ranging from 43% to 70%.[8] The following cognitive domains are frequently impaired: memory processing speed,

attention/concentration, and executive functioning.[9] Cognitive impairments are associated with reduced functional status in MS and have a deleterious impact on individual's personal, occupational, and social functioning, and on the comprehensive quality of life.[10] Cognitive abilities play a major role also in motor performance and in balance control, however, the role of higher cognitive processes on balance efficacy in PwMS has been poorly and not been extensively investigated.[11] Besides, the comprehensive link between attention and motor-action has been supported by several studies.[12] Selective attention allows the execution of a correct motor response by selecting relevant information about the task, the distractors, the goals, between competing sources is therefore essential for the action planning. Concerning the cognitive-motor interference (CMI), this relation is directly measurable by the dual-task cost (DTC),[13,14] investigated in PwMS through the Stroop Test somministration.[15] Dual task perfomance is the capacity to do two tasks simultaneously, the subject's attention is drawn to an external source of attention while the primary task is ongoing. Concerning the constrained action hypothesis, this attentional change may lead motor systems to react automatically, thus increasing the performance effectiveness.[16] The processing capacity required for doing successfully dual-task activities may be affected by the presence of cognitive impairments.[17] It is plausible that motor deficits enhance the cognitive demands necessary to execute functional movements, and the concurrent performance of tasks may exceed cognitive processing abilities.[18] Considering that dual tasking is frequently impaired in MS and its strong impact on activities of daily living (ADL),[8] rehabilitative treatment does not have to consider separately the motor and cognitive aspects.

In recent years, Virtual Reality (VR) technologies have begun to be used as a treatment tool in rehabilitation given their low-cost, high portability, off-the-shelf nature, and ability to deliver engaging, high-repetitive, task-oriented, standardized, active learning therapies.[19] Moreover, PwMS defined their experience of gaming as fun, challenging, and self-motivating, key elements for a successful motor learning.[20]

The evidence of interactive video-game therapeutic exercises for improving balance and motor functions in PwMS were inconclusive, even if few studies showed a possible positive effect on balance and cognitive functions such as processing speed.[21–24]

However, the aforementioned studies did not investigate the effects on motor and cognitive functions simultaneously in comparison to conventional instrumental balance training.

Aims

The main objective of this study will be to test the effects of a commercially available VGT (Xbox Kinect) on balance and dual-tasking ambulatory PwMS compared to a standardized balance platform training (BPT). We hypothesize that the VGT, and in particular "action video games", would improve balance and cognitive function more than BPT. We hypothesize that VGT would activate those cognitive components of learning more than BPT, leading to an improvement in balance and divided attention under multi-task conditions in a sample of MS patients.

METHODS AND ANALYSIS

Study design and setting

This is a parallel-assignment, double-blinded randomized control trial. The outcome assessor and the data analyst will be blinded to the group allocation of participants. PwMS who meet the inclusion criteria and provide written informed consent will be assigned to one of the two treatments, the Video Game Therapy (VGT) or the Balance Platform Training (BPT). This study was approved by the Ethics Committee of Ferrara with approval number 170691. The trial protocol has been registered on ClinicalTrials.gov (NCT03353974)

The protocol of this clinical trial is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[25] A SPIRIT Checklist is

available as additional file (Additional file 1). Subjects will be recruited from the patients afferent to Outpatient Rehabilitation Clinic at University Hospital of Ferrara.

Selection criteria and recruitment of participants

People affected by MS will be included if they meet the following inclusion criteria:

- Men and women, aged 18 to 60 years;
- Diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding 3 months;
- Disability rate defined by EDSS score from 4 to 5.5;[26]
- Balance impairments with increased fall risk, defined as TUG > 8.4s;[27]
- Mini Mental Status Examination (MMSE) score ≥24/30.[28]

Exclusion criteria will be:

- Other (neurological) conditions that may affect motor function;
- Visual impairments (daltonism and visual acuity deficit);
- Medical conditions that might interfere with the ability to complete the study protocol safely.

During the first appointment, potential participants will be informed about all the study procedures and screened following the aforementioned inclusion criteria. If they meet inclusion criteria and are interested in taking part to the study, the physician will give them a letter explaining study purpose and procedures, time commitments, risks, potential benefits, treatment alternatives and study staff contact information, as well the Consent Form. In the following 3 days, the potential participant will be contacted and asked about its decision; if the subject decide to take part to the study, the research staff will give it an appointment for the consign to the signed Consent Form and for the baseline outcome measures, conducted by a physiotherapist. If the subject rejects the participation to the study, the research staff remains available for every further information. The total number of subjects screened for participation and the number of subjects who decline to participate will be recorded, according to the Consolidate Standards of Reporting Trials (CONSORT) guidelines.[29] (Figure 1)

Randomization and blinding

People meeting inclusion criteria who decided to participate, will be assigned to one of the two treatment groups through a block randomization approach (1:1 ratio). The randomization scheme will be set up in permuted blocks of 4 to ensure a similar number of participants between groups. The randomization scheme will be generated by using the web site Randomization.com (http://www.randomization.com) and managed by an administrator external to research group in order to prevent any selection bias. Outcome assessor will be blinded about subject's group allocation. All outcome data and group of assignment will be managed in different dataset in order to maintain the blinding during data analysis. The privacy of the participants and their personal medical records will be guaranteed by treating the data according to the Italian Law n. 196/2003, to the "Safe Harbor Act" (2000/520/CE) and to the "European Union Data Protection Directive (95/46/EC 24 October 1995)."

Intervention

All participants will receive twelve 1-h training session over 4 weeks, resulting in a three sessions/week scheme. In order to manage possible absence lasting one or more treatment sessions, a potential window of 5 weeks will be set to ensure the achievement of all 12 sessions. Subjects who miss a training session will be contacted by phone to determine reasons of the absence and to

maintain adherence to following treatment sessions. Subjects who miss more than three consecutive treatment sessions will be excluded from the study.
Every training session consists of about fifty minutes of exercise and about ten minutes of mobility and flexibility activity to prevent muscle soreness due to movement.

Video-game Therapy (VGT)
VGT will be delivered with a commercial video game console (X-Box 360 Kinect, Microsoft, Inc., Redmond, WA). Pre-selected games were chosen from "Kinect Adventures" and "Kinect Sports" that encompassed a wide range of motor activities in a standing position. Specifically, balance and mobility related motor tasks, such as side stepping, lateral weight shifting, jumping, walking (lateral, forward and backward) and arm goal reaching were trained.
Kinect is a commercial device, therefore calibration of the instrument on the individual patient is not provided. The physiotherapy treatment with this device will be set by the physiotherapist basing on clinical observations of patient's characteristics, preferences and level of functioning.
During the first session, a list of games will be tested according to the patient's abilities and preferences. In the following sessions, games will be proposed with a randomized practice approach, progression proceed over time according to the patients' motor and balance improvements. Each task will consist of 2–5 minutes of training and rest period will be given if necessary. During sessions, the patients will be carefully supervised by a physiotherapist who monitored the patient's safely (e.g., risk of falls, impulsive reactions). The physiotherapist will give also performance feedback, in addition to whose provided by VGT: visual and augmented (knowledge of both results and performance).[30]

Balance Platform Therapy (BPT)
Balance/rebalancing, postural stability and weight-shifting exercises with and without visual feedback were administered using a Balance Platform (Biodex Medical Systems, Inc., Shirley, NY) that had been previously tested in multiple sclerosis patients. Each task will be trained for about 2-3 minutes and followed by a rest period when necessary. During the first session, the tasks will be set to an "entry level," and the exercise progression will be adjusted over time according to the patient's capabilities (intermediate and difficult level). BPT offers visual feedback about reaching of goals (augmented feedback). The physiotherapist will provide additional external feedback during the activities.

Concomitant care and recommendations
All the subjects will be advised to not undertake other physical treatments until the end of the assessment period. Subjects will be also exhorted to not use the videogame console at home for leisure, in order to prevent confounding effects. It will be asked to patients to wear the same shoes and orthosis during all the outcome assessment and training sessions.

Intervention fidelity and monitoring of adverse events
All the interventions will be delivered by a physiotherapist with at least 5 years of experience in treatment of PwMS, properly formed about VGT or BPT. Training sessions features and comments will be tracked in a precompiled form. Any adverse unpredictable event will be recorded in the patient's registry and in the electronic study database. Their management will be in agreement to the related hospital policies, with referral for appropriate medical follow-up.

Outcome assessment and data collection
All the clinical evaluations will be performed at the Ferrara University Hospital by the same blinded assessor at the three time-point evaluations: (T0) baseline, prior to the first intervention; (T1) end of treatment, after the twelve therapy sessions; (T2) follow up, three months after the end of treatment.
Clinical and posturoghraphic assessment will be delivered by a physiotherapist properly trained

about evaluation procedures. Cognitive tests will be delivered by a neuropsychologist with years of experience in assessment and treatment of PwMS. A physician member of the research team will define the patient's EDSS score. A member of the team will record the general demographic information (age, gender), comorbidities and medical history of every participants. A summary of the study plan is reported in Table 1.

Table 1 Schedule of enrollment, interventions and assessments

	Study period				
	Enrollment	Allocation	Post allocation		Close-out
Timepoint	T-1		T0	T1	T2
Enrollment					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Interventions					
Video-game therapy			◆———		
Balance platform therapy			◆———		
Assessments					
Primary outcome					
Timed Up and Go test			X	X	X
Secondary outcome					
Clinical measures and questionnaires			X	X	X
Cognitive and psychological assessment			X	X	X
Posturographic assessment			X	X	X

Abbreviations: T-1 enrollment, T0 before treatment, T1 after treatment, T2 3-month follow-up

Primary outcome: Balance

This function will be assessed by the Timed Up and Go (TUG) test, a reliable and valid performance-based measure of balance and functional mobility.[27] The patient will be instructed to stand up from a chair, walk for three meters, cross a line marked on the floor, turn around, walk back and sit down. The time used to complete the task is recorded using a chronometer. During the assessment the subject is allowed to use any necessary gait aid (not physical assistance). In order to reduce variability due to subject's fatigue, this test will be the first performed during assessment session. The TUG test will be repeated three times and mean value will be recorded.

Secondary outcome measures

Secondary outcomes will include: (1) clinical measures and questionnaires, (2) cognitive and psychological assessment, (3) posturographic assessment

Clinical measures and questionnaires:

a. Dynamic Gait Index (DGI): gait, balance and risk of fall are measured using DGI. DGI will not evaluate only usual steady-state walking, but also walking during more challenging task (i.e. cross obstacles, slalom). Eight functional walking tests will be performed by the subject and scored out of three (maximum total score is 24).[31]
b. Four Square Step Test (FSST): this timed test is intended to challenge the rapid change in direction while stepping forward, backward and sideways over a low obstacle. The faster the time measured to perform the task, signifies a superior level of dynamic balance abilities. The

minimal detectable change estimate for the FSST in MS is 4.6 s and it was found to be a valid assessment tool in MS.[32]

c. Functional Reach Test (FRT): this test assesses the subject's stability by measuring the maximum distance an individual can reach forward while standing in a fixed position. A longer reaching distance indicates better postural control.[33]
d. Multiple Sclerosis Impact Scale – 29 (MSIS-29): this health-rated quality of life questionnaire assesses the impact of MS on physical and psychological functions. It is formed by 29 items on ADL I and II: 20 about physical activity and 9 of psychological status of the person. Each item can be scored with a value from 0 to 5; total score is given by the sum of all the items and then is transformed in a range from 0 to 100.[34]
e. Multiple Sclerosis Walking Scale – 12 (MSWS-12): this questionnaire assesses the impact of MS on walking ability. It is formed by 12 items, asking the patient about his perception on gait speed, running, confidence ascending/discending stairs, balance and fatigue. The total score is obtained by the sum of the score of each item (0-5) and then transformed into a value from 0 to 100.[35]
f. Modified Fatigue Impact Scale (MFIS): this 21-item questionnaire assesses the perceived impact of fatigue on the subscale physical, cognitive, and psychological functioning during the past 4 weeks. MFIS has been recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines.[36,37]

Cognitive and psychological assessment

a. Beck Depression Inventory – Second Edition (BDI-II): this is a 21 item self-report measure that quantifies severity of depression and over behavioral characteristics of depression.[38]
b. State Trait Anxiety Inventory (STAI-Y): this self-report questionnaire measures the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious. There are 2 subscales: 20 items allocated to each of the State Anxiety (S-Anxiety) and Trait Anxiety (T-Anxiety).[39]
c. Test of Attentional Performance (T.A.P. version 2.3): attentional performance will be evaluated using a neuropsychological computer test. Errors, omissions, and reaction times (RTs) will be recorded as outcomes of performance. Three modules of the T.A.P will be administered: Go-No Go subtest as it allows assessment of the specific ability of subjects to suppress undesired responses; alertness subtest that measure the simple reaction time in response to a visual stimulus and, divided attention subtest, that explored with "dual-task" test the ability to attend simultaneously two stimuli (visual and acoustic) processed in parallel.[40]
d. Stroop Color-Word Test (SCWT): this neuropsychological test is used to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute. Subjects are required to read three different tables as fast as possible. Two of them represent the "congruous condition" in which participants are required to read names of colors printed in black ink and name different color patches. Conversely, the third table represent the incongruent condition, in which participants are required to name the color of the ink instead of reading the word.[41]
e. Symbol Digit Modalities Test (SDMT): this neuropsychological test is used to quantify the cognitive processing speed. It consists of orally report the correct number corresponding to a symbol in a pseudorandom sequence of nine symbol as quickly as possible.[42]

Posturographic assessment

Instrumented basic balance evaluation (IBBE): Force platform measurement are routinely used as objective markers of subjects' balance ability. Several parameters can be extracted from the force platforms that correlate with balance ability and risk of falls in PwMS. During the instrumented

tasks, subjects will be asked to stand on a force plate (BERTEC Model 4080–10, BERTEC, USA) with the arms parallel to their body. Each subject will undergo 5 repetitions (each lasting 60 seconds) of two tasks that will consist in standing with the eyes open and standing with the eyes closed. The movements of the Center of Pressure (CoP) of the subjects will be recorded and a series of features will be extracted from the CoP traces to inform on different balance characteristics of each patient and on the specific effect of each of the proposed therapies. Features that will be analyzed include different measures of CoP displacement in the antero-posterior (AP) and medio-lateral (ML) directions, the CoP path length (total, AP and ML) and the CoP average and maximum speed.[30]
Dual-tasking assessment will be performed combining posturographic and neuropsychological tests: subjects will be asked to complete SCWT standing on force platform. Ability to inhibit cognitive interferences during quiet and standing condition will be compared.

Data management
Data analysis will be performed according to the research hypothesis mentioned. Stata Statistical Software (Release 13.1. College Station, TX: StataCorp LP, USA) will be used for data analysis

Sample size and power
The primary outcome for this study is to highlight differences in the time used to perform TUG test, between PwMS who underwent VGT and BPT. Our preliminary results from unpublished pilot study shown a VGT effect size of 0.93 in people with MS and EDSS < 6. Given equal allocation between treatment and control arms, ad using 80% power and alpha of 5%, we would need 40 subjects to complete the study. Conservatively, we expect a 10% rate of drop-out, thus the sample size will be increased by 10% to 48 subjects (24 per arm).

Statistical analyses
Descriptive statistics (mean and standard deviation) will be reported before treatment, after treatment, and at three months follow-up for all the selected variables (clinical, instrumental and questionnaires). Between-group differences will be explored with the Wilcoxon rank-sum test. Moreover, a repeated-measures analysis of variance (within-group factor: TIME; between-group factor: TREATMENT) will be conducted to detect main effects for treatment and time for all the available outcomes; results will be reported as mean and 95% CI. Significance will be recognized for $p < 0.05$.

Intention-to-treat
Every attempt will be made to avoid missing data through a careful check of self-reported measures, as self-administered questionnaires. An intention-to-treat analysis was carried out on all outcome measures. Missing data will be treated using the last observation carried forward approach.

Data monitoring and interim analysis
The trial does not include Data Monitoring Committee. An update on trial progress will be shared to Ferrara University Hospital Research office every six months. The research coordinator will be responsible for interim analysis to determine if the trial should stop, modify or carried out. Any subsequent modifications will be discussed within the research group and communicated to the funding agency and Ethic Committee.

Patient and Public Involvement
The research question in this study starts from years of experience in rehabilitation of PwMS and previous research study on use of video game therapy in balance impairment. The drafting of the study was submitted to Multiple Sclerosis Italian Society (FISM) and reviewed to better meet

patients' needs. The final version of the study reflects the collaboration between the research group and the patients' association.

Dissemination plan
Communication of results and conclusions of this trial will be assigned to high-quality journals and national and international conferences. Results will also be disseminated through FISM annual conference. People with MS will be informed about possible efficacy of proposed treatment through MS support groups.

DISCUSSION

This trial may highlight the role of gaming in the rehabilitation of PwMS, enforcing utilization of new technologies in daily clinical practice among subjects with mild to moderate disability.
Our expectation from the proposed research, is to observe a greater effect on mobility, balance and dual-tasking through virtual reality training compared to a conventional approach. The possibility to make rehabilitative session more engaging for patients may increase involvement and adherence in rehabilitation process. Moreover, virtual reality-based rehabilitation typically provides augmented feedback during training that can contribute to learning motor skills more effectively. The virtual reality effect to create a challenging environment may be exploited to manage neuropsychological impairments, like attentional deficit or impaired alertness. Therefore, we expect to observe greater modifications on cognitive and psychological evaluation of people who received rehabilitation through video-game platform. Recently, gaming consoles introduced in clinical and research settings may represent a low-cost opportunity of delivering virtual-reality training. For this reason, the use of VGT may be delivered at home, promoting self-management strategies to improve mobility function and long-term outcomes. However, further studies will be necessary to confirm the results related to physical and neuropsychological outcomes.

Authors' contributions
AB, GF, GS, GZ, GM, ABe, SS developed the trial protocol. All authors have read and approved the final manuscript.

Funding statement
This research was supported by the Multiple Sclerosis Italian Society (Grant 2018/R/19).

Competing interests
The authors declare that they have no competing interests.

REFERENCES

1 Organization WH, Federation MSI. *Atlas : multiple sclerosis resources in the world 2008*. World Health Organization 2008.

2 Khan F, Amatya B. Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. *Arch Phys Med Rehabil* 2017;**98**:353–67. doi:10.1016/j.apmr.2016.04.016

3 Cameron MH, Nilsagard Y. Balance, gait, and falls in multiple sclerosis. *Handb Clin Neurol* 2018;**159**:237–50. doi:10.1016/B978-0-444-63916-5.00015-X

4 Martin CL, Phillips BA, Kilpatrick TJ, *et al.* Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler Houndmills Basingstoke Engl* 2006;**12**:620–8. doi:10.1177/1352458506070658

5 Prosperini L, Sbardella E, Raz E, *et al.* Multiple sclerosis: white and gray matter damage associated with balance deficit detected at static posturography. *Radiology* 2013;**268**:181–9. doi:10.1148/radiol.13121695

6 Fitzpatrick R, McCloskey DI. Proprioceptive, visual and vestibular thresholds for the perception of sway during standing in humans. *J Physiol* 1994;**478 (Pt 1)**:173–86. doi:10.1113/jphysiol.1994.sp020240

7 Cameron MH, Lord S. Postural control in multiple sclerosis: implications for fall prevention. *Curr Neurol Neurosci Rep* 2010;**10**:407–12. doi:10.1007/s11910-010-0128-0

8 Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008;**7**:1139–51. doi:10.1016/S1474-4422(08)70259-X

9 Giazkoulidou A, Messinis L, Nasios G. Cognitive functions and social cognition in multiple sclerosis: An overview. *Hell J Nucl Med* 2019;**22 Suppl**:102–10.

10 Chalah MA, Ayache SS. Deficits in Social Cognition: An Unveiled Signature of Multiple Sclerosis. *J Int Neuropsychol Soc JINS* 2017;**23**:266–86. doi:10.1017/S1355617716001156

11 Negahban H, Mofateh R, Arastoo AA, *et al.* The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture* 2011;**34**:479–84. doi:10.1016/j.gaitpost.2011.06.023

12 Song J-H. The role of attention in motor control and learning. *Curr Opin Psychol* 2019;**29**:261–5. doi:10.1016/j.copsyc.2019.08.002

13 Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2015;**21**:123–31. doi:10.1177/1352458514547408

14 Chamard Witkowski L, Mallet M, Bélanger M, *et al.* Cognitive-Postural Interference in Multiple Sclerosis. *Front Neurol* 2019;**10**:913. doi:10.3389/fneur.2019.00913

15 Ruggieri S, Fanelli F, Castelli L, *et al.* Lesion symptom map of cognitive-postural interference in multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2018;**24**:653–62. doi:10.1177/1352458517701313

16 Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Interv Aging* 2017;**12**:557–77. doi:10.2147/CIA.S125201

17 Tombu M, Jolicoeur P. A central capacity sharing model of dual-task performance. *J Exp Psychol Hum Percept Perform* 2003;**29**:3–18. doi:10.1037//0096-1523.29.1.3

18 Mulder T, Zijlstra W, Geurts A. Assessment of motor recovery and decline. *Gait Posture* 2002;**16**:198–210. doi:10.1016/s0966-6362(01)00157-6

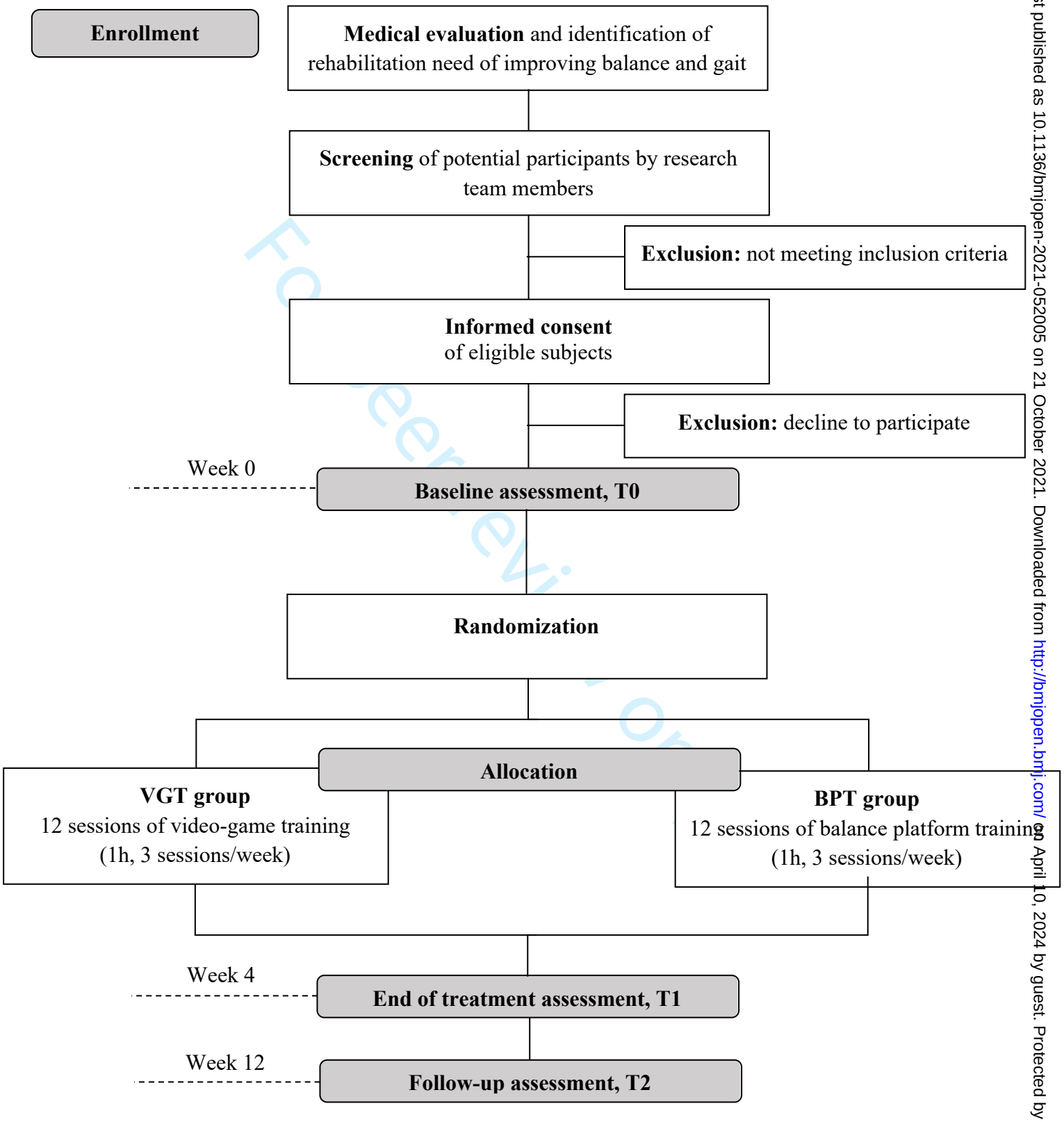
19 Laver KE, Lange B, George S, *et al.* Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev* 2017;**11**:CD008349. doi:10.1002/14651858.CD008349.pub4

20 Forsberg A, Nilsagård Y, Boström K. Perceptions of using videogames in rehabilitation: a dual perspective of people with multiple sclerosis and physiotherapists. *Disabil Rehabil* 2015;**37**:338–44. doi:10.3109/09638288.2014.918196

21 Parra-Moreno M, Rodríguez-Juan JJ, Ruiz-Cárdenas JD. Use of commercial video games to improve postural balance in patients with multiple sclerosis: A systematic review and meta-

analysis of randomised controlled clinical trials. *Neurol Barc Spain* Published Online First: 7 March 2018. doi:10.1016/j.nrl.2017.12.001
22 Brichetto G, Spallarossa P, de Carvalho MLL, *et al.* The effect of Nintendo® Wii® on balance in people with multiple sclerosis: a pilot randomized control study. *Mult Scler Houndmills Basingstoke Engl* 2013;**19**:1219–21. doi:10.1177/1352458512472747
23 Pitteri M, Dapor C, Ziccardi S, *et al.* Visual-Attentional Load Unveils Slowed Processing Speed in Multiple Sclerosis Patients: A Pilot Study with a Tablet-Based Videogame. *Brain Sci* 2020;**10**. doi:10.3390/brainsci10110871
24 Bove R, Rowles W, Zhao C, *et al.* A novel in-home digital treatment to improve processing speed in people with multiple sclerosis: A pilot study. *Mult Scler Houndmills Basingstoke Engl* 2021;**27**:778–89. doi:10.1177/1352458520930371
25 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586. doi:10.1136/bmj.e7586
26 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**:1444–52. doi:10.1212/wnl.33.11.1444
27 Kalron A, Dolev M, Givon U. Further construct validity of the Timed Up-and-Go Test as a measure of ambulation in multiple sclerosis patients. *Eur J Phys Rehabil Med* 2017;**53**:841–7. doi:10.23736/S1973-9087.17.04599-3
28 Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* 1992;**40**:922–35. doi:10.1111/j.1532-5415.1992.tb01992.x
29 Moher D, Schulz KF, Altman DG, *et al.* The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Clin Oral Investig* 2003;**7**:2–7. doi:10.1007/s00784-002-0188-x
30 Straudi S, Severini G, Sabbagh Charabati A, *et al.* The effects of video game therapy on balance and attention in chronic ambulatory traumatic brain injury: an exploratory study. *BMC Neurol* 2017;**17**:86. doi:10.1186/s12883-017-0871-9
31 Forsberg A, Andreasson M, Nilsagård YE. Validity of the dynamic gait index in people with multiple sclerosis. *Phys Ther* 2013;**93**:1369–76. doi:10.2522/ptj.20120284
32 Dite W, Temple VA. A clinical test of stepping and change of direction to identify multiple falling older adults. *Arch Phys Med Rehabil* 2002;**83**:1566–71. doi:10.1053/apmr.2002.35469
33 Duncan PW, Weiner DK, Chandler J, *et al.* Functional reach: a new clinical measure of balance. *J Gerontol* 1990;**45**:M192-197. doi:10.1093/geronj/45.6.m192
34 Hobart J, Lamping D, Fitzpatrick R, *et al.* The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain J Neurol* 2001;**124**:962–73.
35 Hobart JC, Riazi A, Lamping DL, *et al.* Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology* 2003;**60**:31–6.
36 Larson RD. Psychometric Properties of the Modified Fatigue Impact Scale. *Int J MS Care* 2013;**15**:15–20. doi:10.7224/1537-2073.2012-019
37 Kos D, Kerckhofs E, Carrea I, *et al.* Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Mult Scler Houndmills Basingstoke Engl* 2005;**11**:76–80. doi:10.1191/1352458505ms1117oa
38 Sica C, Ghisi M. The Italian versions of the Beck Anxiety Inventory and the Beck Depression Inventory-II: Psychometric properties and discriminant power. In: *Leading-Edge Psychological Tests and Testing Research*. 2007. 27–50.
39 Santangelo G, Sacco R, Siciliano M, *et al.* Anxiety in Multiple Sclerosis: psychometric properties of the State-Trait Anxiety Inventory. *Acta Neurol Scand* 2016;**134**:458–66. doi:10.1111/ane.12564
40 Zimmermann P, Fimm B. A test battery for attentional performance. In: *Applied Neuropsychology of Attention. Theory, Diagnosis and Rehabilitation*. 2002. 110–51.
41 Scarpina F, Tagini S. The Stroop Color and Word Test. *Front Psychol* 2017;**8**. doi:10.3389/fpsyg.2017.00557

42 Nocentini U, Giordano A, Di Vincenzo S, *et al.* The Symbol Digit Modalities Test - Oral version: Italian normative data. *Funct Neurol* 2006;**21**:93–6.



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**1, 3**
	2b	All items from the World Health Organization Trial Registration Data Set	**-**
Protocol version	3	Date and version identifier	**8**
Funding	4	Sources and types of financial, material, and other support	**8**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 2, 8**
	5b	Name and contact information for the trial sponsor	**1**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**8**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**7, 8**

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

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**7**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**2**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**3**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**3**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**3**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**3**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**3**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**5**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**4**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**7**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**7**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**7**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**7**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**7**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**7**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**4, 7**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**7**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**3**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**-**

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**2, 3**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**not applicable**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**3**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**8**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**-**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**not applicable**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**8**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**not present**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**not present**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**sent to editorial office_**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**not applicable**

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

BMJ Open

The role of video games therapy on balance and dual tasking in multiple sclerosis. Study protocol for a randomized controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052005.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Aug-2021
Complete List of Authors:	Baroni, Andrea; Ferrara University Hospital, Department of Neuroscience and Rehabilitation Fregna, Giulia; Ferrara University Hospital, Department of Neuroscience and Rehabilitation Milani, Giada; University of Ferrara, Doctoral Program in Translational Neurosciences and Neurotechnologies Severini, G; University College Dublin, School of Electrical and Electronic Engineering Zani, Giulia; Ferrara University Hospital, Department of Neuroscience and Rehabilitation Basaglia, Nino; University of Ferrara, Department of Neuroscience and Rehabilitation Straudi, Sofia; University of Ferrara, Department of Neuroscience and Rehabilitation
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, REHABILITATION MEDICINE, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The role of video games therapy on balance and dual tasking in multiple sclerosis. Study protocol for a randomized controlled trial.

Andrea Baroni[1], PhD, Giulia Fregna[1], MS, Giada Milani[1,2], MS, Giacomo Severini[3], PhD, Giulia Zani[1], MS, Nino Basaglia[1], MD, Sofia Straudi[1,4], MD, PhD

Affiliations:

[1] Department of Neuroscience and Rehabilitation, Ferrara University Hospital, Ferrara, Italy

[2] Ferrara University, Doctoral Program in Translational Neurosciences and Neurotechnologies, Ferrara, Italy

[3] School of Electrical and Electronic Engineering, University College Dublin, Dublin, Ireland

[4] Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy

Correspondence

Dr. Sofia Straudi, MD, PhD. Neuroscience and Rehabilitation Department, Ferrara University Hospital. Via Aldo Moro 8, 44124 Cona, Ferrara, Italy. s.straudi@ospfe.it 0039 0532236953

ABSTRACT

Introduction Multiple Sclerosis (MS) is one of the major causes of disability in young adults and influences balance, with a poor outcome on daily living activities and participation in social life. The cognitive domain is frequently impaired in people with MS (PwMS), particularly the capacity to perform dual-task activities. Impaired cognitive processing abilities need to be treated, and motor and cognitive aspects are not considered separately. Recently, video-game therapy (VGT) has been used in rehabilitation to improve motor outcomes and cognitive processing speed. The aim of this study is to test the efficacy of commercially available VGT on balance and dual tasking in PwMS compared to standardized balance platform training (BPT).

Methods and analysis This will be a parallel-assignment, double-blinded randomized control trial. Forty-eight (24 per arm) PwMS (EDSS 4-5.5) will be randomly assigned to receive 1-h training session over four weeks (three sessions/week) of either: (1) VGT on commercial video game console to train balance and mobility-related activities or (2) BPT to perform balance, postural stability and weight-shifting exercises with and without visual feedback. The same assessor will evaluate outcome measures at points: before and after the twelve training sessions and at three months of follow-up. The primary outcome is balance, assessed by the Timed Up and Go (TUG) test. We will also evaluate gait, risk of fall, fatigue and health-related quality of life as well as cognitive and psychological aspects (depression, anxiety and attentional performance) and stability through posturographic evaluation. Dual-tasking assessment will be performed combining posturographic and neuropsychological tests. Data analysis will be performed to compare the efficacy of the two treatments.

Ethics and dissemination Ethical approval have been granted from the local Ethics Committee. Study results will be communicated through high-quality journals and national and international conferences.

Trial registration ClinicalTrials.gov, Identifier: NCT03353974

Keywords Multiple sclerosis, video-game, balance, dual-task

Strengths and limitations of this study

- This trial will use objective evaluation as a posturographic assessment to test balance and dual-task.
- Motor and cognitive outcomes will be assessed separately and in association.
- Results from this trial will need a larger sample to be confirmed.
- This study protocol includes only young subjects (aged under 60) with good comprehensive functioning.
- This study does not analyze long-term effects (over three months).

INTRODUCTION

Multiple Sclerosis (MS) is characterized by multifocal inflammatory demyelinated plaques distributed over time and space within the Central Nervous System (CNS). It affects approximately 1.3 million people worldwide and is a major cause of chronic neurological disability in young adults aged 18–50 years.[1,2] Deficits in balance control and cognition are prevalent impairments in people with MS (PwMS) [3], even at an early stage and without clinical disability.[4] Previous studies have reported that 30 to 63% of PwMS experience a fall event between 1 and 12 months since the onset of the disease.[5] Balance maintenance is a complex task that depends on the continuous flow of proprioceptive information from the muscles, tendons, joints, skin, vestibular and visual systems toward the CNS.[3] In PwMS, the extended damage caused in the CNS leads to a decreased ability in integrating the afferent proprioceptive information, thus negatively influencing postural response and the capability to maintain balance safely.[5,6] Balance impairment can consistently limit the activities of daily living and the active participation in social life.

Cognitive impairment is various among PwMS, with current prevalence rates ranging from 43% to 70%.[7] The following cognitive domains are frequently impaired: memory processing speed, attention/concentration, and executive functioning.[8] Cognitive impairments are associated with reduced functional status in MS. They have a deleterious impact on the individual's personal, occupational, and social functioning and the comprehensive quality of life.[9]

The role of cognitive functioning on motor performance and balance control is widely known.[10] However, the effects of impaired cognitive processes on balance efficacy have not been extensively investigated in PwMS.[11] Besides, the comprehensive link between attention and motor-action has been supported by several studies.[12] Selective attention allows the execution of a correct motor response by selecting relevant information between the task and the distractors, and it is essential for action planning. Concerning the cognitive-motor interference (CMI), this relation is directly measurable by the dual-task cost (DTC) [13,14], investigated in PwMS through the Stroop Test.[15] Dual-task performance is the capacity to do two tasks simultaneously. The subject's attention is drawn to an external source of attention while the primary task is ongoing. Concerning the constrained action hypothesis, this attentional change may lead motor systems to react automatically, thus increasing the performance effectiveness.[16] The processing capacity required for doing dual-task activities may be affected by cognitive impairments.[17] It is plausible that motor deficits enhance the cognitive demands necessary to execute functional movements, and the concurrent performance of tasks may exceed cognitive processing abilities.[18] Considering that dual tasking is frequently impaired in MS and its strong impact on activities of daily living (ADL) [7], rehabilitative treatment does not have to consider the motor and cognitive aspects separately.

In recent years, active video games technologies have begun to be used as a treatment tool in rehabilitation given their low-cost, high portability, off-the-shelf nature, and ability to deliver engaging, high-repetitive, task-oriented, standardized, active learning therapies.[19] Moreover, PwMS defined gaming experience as fun, challenging, and self-motivating, critical elements for successful motor learning.[20] Active video games' multisensory feedback provided to patients may potentiate the use-dependent plasticity processes in the sensorimotor cortex, promoting functional recovery.[21]

The evidence of interactive video-game therapeutic exercises for improving balance and motor functions in PwMS were inconclusive, even if few studies showed a possible positive effect on balance and cognitive functions such as processing speed.[22–25] Furthermore, patients' motivation seems to be capable of being increased during active video game rehabilitation, allowing patients to exercise more consistently.[21]

All previous studies did not investigate the effects on motor and cognitive functions simultaneously, particularly when compared to conventional instrumental balance training.

Aims

The main objective of this study will be to test the effects of a commercially available VGT (Xbox Kinect) on balance and dual-tasking ambulatory PwMS compared to a standardized balance platform training (BPT). We hypothesize that the VGT, particularly "action video games", would improve balance and cognitive function more than BPT due to the video game's augmented feedback in terms of intensity and type. Furthermore, VGT would activate those cognitive components of learning through a more challenging rehabilitative approach.

METHODS AND ANALYSIS

Study design and setting

This is a parallel-assignment, double-blinded randomized control trial. The outcome assessor and the data analyst will be blinded to the group allocation of participants. PwMS who meet the inclusion criteria and provide written informed consent will be assigned to two treatments, the Video Game Therapy (VGT) or the Balance Platform Training (BPT). The trial protocol has been registered on ClinicalTrials.gov (NCT03353974).

The protocol of this clinical trial is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[26] A SPIRIT Checklist is available as an additional file (Additional file 1). Subjects will be recruited from the patients afferent to Outpatient Rehabilitation Clinic at University Hospital of Ferrara. Patients' recruitment started on 1st December 2017, and it's going to finish on 1st October 2022.

Selection criteria and recruitment of participants

People affected by MS will be included if they meet the following inclusion criteria:

- Men and women, aged 18 to 60 years;
- Diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding three months;
- Disability rate defined by EDSS score from 4 to 5.5 [27];
- Balance impairments with increased fall risk, defined as TUG > 8.4s [28];
- Mini Mental Status Examination (MMSE) score ≥24/30.[29]

Exclusion criteria will be:

- Other (neurological) conditions that may affect motor function;
- Visual impairments (daltonism and visual acuity deficit);
- Medical conditions might interfere with the ability to complete the study protocol safely.

During the first appointment, potential participants will be informed about all the study procedures and screened following the inclusion criteria. Suppose they meet inclusion criteria and are interested in taking part in the study. In that case, the physician will give them a letter explaining study purpose and procedures, time commitments, risks, potential benefits, treatment alternatives, study staff contact information and the Consent Form. A copy of the Consent Form is available as an additional file (Additional file 2). In the following three days, the potential participant will be contacted and asked about its decision; if the subject decides to take part in the study, the research staff will give him/her an appointment for the consign to the signed Consent Form and for the baseline outcome measures, conducted by a physiotherapist. If the subject rejects participation in the study, the research staff remains available for further information. The total number of subjects screened for participation and the number of subjects who decline to participate will be recorded, according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1).[30]

Randomization and blinding

People meeting inclusion criteria who decided to participate will be assigned to one of the two treatment groups through a block randomization approach (1:1 ratio). The randomization scheme will be set up in permuted blocks of 4 to ensure a similar number of participants between groups. The randomization scheme will be generated using the website Randomization.com (http://www.randomization.com) and managed by an external administrator to the research group to prevent selection bias. The outcome assessor will be blinded about the subject's group allocation. All outcome data and assignment groups will be organised in different datasets to maintain the blinding during data analysis. The privacy of the participants and their medical records will be guaranteed by treating the data according to the Italian Law n. 196/2003, to the "Safe Harbor Act" (2000/520/CE) and to the "European Union Data Protection Directive (95/46/EC 24 October 1995)."

Intervention

All participants will receive twelve 1-h training sessions over four weeks, resulting in a three sessions/week scheme. To manage possible absence lasting one or more treatment sessions, a potential window of 5 weeks will be set to ensure the achievement of all 12 sessions. Subjects who miss a training session will be contacted by phone to determine the absence's reasons and maintain adherence to following treatment sessions. Subjects who miss more than three consecutive treatment sessions will be excluded from the study.

Every training session consists of about fifty minutes of exercise and about ten minutes of mobility and flexibility activity to prevent muscle soreness due to movement. All interventions will be delivered at the Rehabilitation Clinic of the University Hospital of Ferrara.

Video-game Therapy (VGT)

VGT will be delivered with a commercial video game console, Kinect for Xbox 360 game system (Microsoft Corporation, Redmond, Washington, USA). Pre-selected games were chosen from "Kinect Adventures!" and "Kinect Sports" (Microsoft Game Studios, Redmond, Washington, USA) that encompassed a wide range of motor activities in a standing position. Specifically, balance and mobility-related motor tasks were trained, such as sidestepping, lateral weight shifting, jumping, walking (lateral, forward and backward), and arm goal reaching.

Kinect is a commercial device therefore calibration of the instrument on the individual patient is not provided. The physiotherapy treatment with this device will be set by the physiotherapist basing on clinical observations of the patient's characteristics, preferences and level of functioning.

A list of games will be tested according to the patient's abilities and preferences. In the following sessions, games will be proposed with a randomized practice approach. Progression proceeds over time according to the patients' motor and balance improvements. Each task will consist of 2–5 minutes of training and a rest period will be given if necessary. During sessions, the patients will be carefully supervised by a physiotherapist who monitored the patient's safety (e.g., risk of falls, impulsive reactions). The physiotherapist will also give performance feedback and those provided by VGT: visual and augmented (knowledge of both results and performance).[31] Despite variability among treatment protocols available in the literature, our treatment dosage in terms of number of sessions and intervention duration is in line with other studies on the efficacy of exergame in people with neurological disorders.[23,32–34]

Balance Platform Therapy (BPT)

Balance/rebalancing, postural stability and weight-shifting exercises with and without visual feedback will be administered using a Balance Platform (Biodex Medical Systems, Shirley, New York, USA) that had been previously tested in MS patients.[35] Each task will be trained for about 2-3 minutes, followed by a rest period when necessary. During the first session, the tasks will be set to an "entry-level". The exercise progression will be adjusted over time according to the patient's capabilities (intermediate and difficult level). BPT offers visual feedback about reaching goals

(augmented feedback). The physiotherapist will carefully supervise the patient and monitor his safety, providing additional external feedback during the activities.

Concomitant care and recommendations

All the subjects will be advised to not undertake other physical treatments until the end of the assessment period. Subjects will also be encouraged to not use the videogame console at home for leisure to prevent confounding effects. It will be asked to patients to wear the same shoes and orthosis during all the outcome assessment and training sessions.

Intervention fidelity and monitoring of adverse events

All the interventions will be delivered by a physiotherapist with at least five years of experience in the treatment of PwMS, properly formed about VGT or BPT. Training sessions features and comments will be tracked in a precompiled form. Any unpredictable adverse events will be recorded in the patient's registry and the electronic study database. Their management will agree with the related hospital policies, with a referral for appropriate medical follow-up.

Outcome assessment and data collection

All the clinical evaluations will be performed at the Ferrara University Hospital by the same blinded assessor at the three time-point evaluations: (T0) baseline, before the first intervention; (T1) end of treatment, after the twelve therapy sessions; (T2) follow up, three months after the end of treatment. Clinical and posturographic assessment will be delivered by a physiotherapist trained adequately about evaluation procedures. A neuropsychologist with years of experience in the assessment and treatment of PwMS will provide cognitive tests. A physician member of the research team will define the patient's EDSS score. A team member will record the general demographic information (age, gender), comorbidities, and medical history of every participant. A summary of the study plan is reported in Table 1.

Table 1 Schedule of enrollment, interventions and assessments

	Study period				
	Enrollment	Allocation	Post allocation		Close-out
Time-point	T-1		T0	T1	T2
Enrollment					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Interventions					
Video-game therapy			◆—	—◆	
Balance platform therapy			◆—	—◆	
Assessments					
Primary outcome					
Timed Up and Go test			X	X	X
Secondary outcome					
Clinical measures and questionnaires			X	X	X
Cognitive and psychological assessment			X	X	X
Posturographic assessment			X	X	X

Abbreviations: T-1 enrollment, T0 before treatment, T1 after treatment, T2 3-month follow-up

Primary outcome: Functional mobility

This function will be assessed by the Timed Up and Go (TUG) test, a reliable and valid performance-based measure of functional mobility.[28] The patient will be instructed to stand up from a chair, walk for three meters, cross a line marked on the floor, turn around, walk back and sit down. The time used to complete the task is recorded using a chronometer. During the assessment, the subject can use any necessary gait aid (not physical assistance). This test will be the first performed during the assessment session to reduce variability due to the subject's fatigue. The TUG test will be repeated three times, and the mean value will be recorded.

Secondary outcome measures

Secondary outcomes will include: (1) clinical measures and questionnaires, (2) cognitive and psychological assessment, (3) posturographic assessment. All secondary outcome measures will be carried out in random order.

Clinical measures and questionnaires:

a. Dynamic Gait Index (DGI): gait, balance and risk of fall are measured using DGI. DGI will evaluate not only usual steady-state walking but also during a more challenging task (i.e. cross obstacles, slalom). The subject will perform eight functional walking tests and score out of three (maximum total score is 24).[36]
b. Four Square Step Test (FSST): this timed test is intended to challenge the rapid change in direction while stepping forward, backward and sideways over a low obstacle. The faster the time measured to perform the task signifies a superior level of dynamic balance abilities. The minimal detectable change estimate for the FSST in MS is 4.6 s, and it was found to be a valid assessment tool in MS.[37]
c. Functional Reach Test (FRT): this test assesses the subject's stability by measuring the maximum distance an individual can reach forward while standing in a fixed position. A longer reaching distance indicates better postural control.[38]
d. Multiple Sclerosis Impact Scale – 29 (MSIS-29): this health-rated quality of life questionnaire assesses the impact of MS on physical and psychological functions. It is formed by 29 items on ADL I and II: 20 about physical activity and nine about psychological status. Each item can be scored with a value from 0 to 5; the total score is given by the sum of all the items and then is transformed in a range from 0 to 100.[39]
e. Multiple Sclerosis Walking Scale – 12 (MSWS-12): this questionnaire assesses the impact of MS on walking ability. It is formed by 12 items, asking the patient about his perception on gait speed, running, confidence ascending/descending stairs, balance and fatigue. The total score is obtained by the sum of the score of each item (0-5) and then transformed into a value from 0 to 100.[40]
f. Modified Fatigue Impact Scale (MFIS): this 21-item questionnaire assesses the perceived impact of fatigue on the subscale physical, cognitive, and psychological functioning during the past four weeks. MFIS has been recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines.[41,42]

Cognitive and psychological assessment

a. Beck Depression Inventory – Second Edition (BDI-II): this is a 21 item self-report measure that quantifies the severity of depression and over behavioural characteristics of depression.[43]
b. State Trait Anxiety Inventory (STAI-Y): this self-report questionnaire measures the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious. There are two subscales: 20 items allocated to each of the State Anxiety (S-Anxiety) and Trait Anxiety (T-Anxiety).[44]

c. Test of Attentional Performance (T.A.P. version 2.3): attentional performance will be evaluated using a neuropsychological computer test. Errors, omissions, and reaction times (RTs) will be recorded as outcomes of performance. Three modules of the T.A.P will be administered: Go-No Go subtest as it allows assessment of the specific ability of subjects to suppress undesired responses; alertness subtest that measures the simple reaction time in response to a visual stimulus and, divided attention subtest, that explored with "dual-task" test the ability to attend simultaneously two stimuli (visual and acoustic) processed in parallel.[45]
d. Stroop Color-Word Test (SCWT): this neuropsychological test is used to assess the ability to inhibit cognitive interference when processing a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute. Subjects are required to read three different tables as fast as possible. Two of them represent the "congruous condition", in which participants are required to read names of colours printed in black ink and name different colour patches. Conversely, the third table represents the incongruent condition, in which participants are required to name the colour of the ink instead of reading the word.[46]
e. Symbol Digit Modalities Test (SDMT): this neuropsychological test quantifies cognitive processing speed. It consists of orally report the correct number corresponding to a symbol in a pseudorandom sequence of nine symbols as quickly as possible.[47]

Posturographic assessment

Instrumented basic balance evaluation (IBBE): Force platform measurements are routinely used as objective markers of subjects' balance ability.[48,49] Several parameters can be extracted from the force platforms that correlate with balance ability and risk of falls in PwMS. During the instrumented tasks, subjects will be asked to stand on a force plate (BERTEC Model 4080–10, BERTEC, Columbus, Ohio, USA) with arms parallel to their body. Each subject will undergo five repetitions (each lasting 60 seconds) of two tasks that will consist in standing with the eyes open and standing with the eyes closed. The movements of the Center of Pressure (CoP) of the subjects will be recorded. A series of features will be extracted from the CoP traces to inform on different balance characteristics of each patient and the specific effect of each of the proposed therapies. Features that will be analyzed include different measures of CoP displacement in the anteroposterior (AP) and mediolateral (ML) directions, the CoP path length (total, AP and ML) and the CoP average and maximum speed.[31]
Dual-tasking assessment will be performed combining posturographic and neuropsychological tests: subjects will be asked to complete SCWT standing on the force platform, ensuring a similar condition to single-task SCWT. The ability to inhibit cognitive interferences during quiet and standing conditions will be compared.

Data management

Data analysis will be performed according to the research hypothesis mentioned. Stata Statistical Software (Release 13.1. College Station, TX: StataCorp LP, USA) will be used for data analysis

Sample size and power

The primary outcome of this study is to highlight differences in the time used to perform the TUG test between PwMS who underwent VGT and BPT. Our preliminary results from an unpublished pilot study shown a VGT effect size of 0.93 in people with MS and EDSS < 6. Given equal allocation between treatment and control arms, ad using 80% power and alpha of 5%, we would need 40 subjects to complete the study. Conservatively, we expect a 10% rate of drop-out. Thus the sample size will be increased by 10% to 48 subjects (24 per arm).

Statistical analyses

Descriptive statistics (mean and standard deviation) will be reported before treatment, after treatment, and at three months follow-up for all the selected variables (clinical, instrumental and questionnaires). Between-group differences will be explored with the Wilcoxon rank-sum test. Moreover, a repeated-

measures analysis of variance (within-group factor: TIME; between-group factor: TREATMENT) will be conducted to detect the main effects for treatment and time for all the available outcomes. To calculate the effect size of both treatments, we will use Cohen's d.[50] Results will be reported as mean and 95% CI. Significance will be recognized for $p < 0.05$.

Intention-to-treat

Every attempt will be made to avoid missing data through a careful check of self-reported measures, as self-administered questionnaires. An intention-to-treat analysis was carried out on all outcome measures. Missing data will be treated using the last observation carried forward approach.

Data monitoring and interim analysis

The trial does not include Data Monitoring Committee. An update on trial progress will be shared with Ferrara University Hospital Research office every six months. The research coordinator will be responsible for interim analysis to determine if the trial should stop, modify or carry out. The research group will discuss any subsequent modifications and communicate to the funding agency and Ethics Committee.

Patient and Public Involvement

The research question in this study starts from years of experience in rehabilitation of PwMS and previous research study on the use of video game therapy in balance impairment. The drafting of the study was submitted to the Multiple Sclerosis Italian Society (FISM) and reviewed to better meet patients' needs. The final version of the study reflects the collaboration between the research group and the patients' association.

Ethics and dissemination

The Ethics Committee of Ferrara approved this study with approval number 170691 on 19th 0ctober 2017. Communication of results and conclusions will be assigned to high-quality journals and national and international conferences. Results will also be disseminated through FISM annual conference. People with MS will be informed about the possible efficacy of the proposed treatment through MS support groups.

DISCUSSION

This trial may highlight the role of gaming in the rehabilitation of PwMS, enforcing the utilization of new technologies in daily clinical practice among subjects with mild to moderate disability.[51]
Our expectation from the proposed research is to observe a more significant effect on mobility, balance and dual-tasking through virtual reality training compared to a conventional approach. A meta-analysis by Casuso-Holgado et al. found that active video game training could be considered as effective as conventional training in improving balance and gait abilities in PwMS, but treatment modalities' variability among the included studies may give rise to various interpretations.[52] Furthermore, we expect different results due to the dosage of our treatment compared to those of included studies in the review and treatment administration modalities that include home-based interventions and one intervention based on telerehabilitation. Instead, our expected results are in line with what was found by Nascimento et al. in their systematic review regarding fatigue, quality of life, and balance.[53] Making the rehabilitative session more engaging for patients may increase involvement and adherence in the rehabilitation process. Increased participation and motivation were already being observed in PwMS treated with gamified training.[51,54] Moreover, virtual reality-based rehabilitation typically provides augmented feedback during training that can contribute to learning motor skills more effectively. Active video games may offer an enriched environment useful for subjects with neuropsychological disorders, like attentional deficit or impaired alertness. Exergaming has recently been studied as an effective strategy to improve dual-task performance in

people with neurological disabilities.[55] Therefore, we expect to observe greater modifications on cognitive and psychological evaluation of people who received rehabilitation through video-game platforms. Recently, gaming consoles introduced in clinical and research settings may represent a low-cost opportunity of delivering virtual-reality training. For this reason, the use of VGT may be delivered at home, promoting self-management strategies to improve mobility function and long-term outcomes. Our study may have several limitations. First, the absence of evaluation over three months couldn't give any information about the long-term effects of active video game training. Second, we won't use any instrument to assess patients' satisfaction with the experimental treatment. Third, any neuroimaging technique will be used to show the possible neuroplastic changes in the brain due to VGT. Finally, we won't study the effects of combined treatment of VGT and other rehabilitative techniques for balance and mobility, despite combining treatments seems to augment training efficacy and boost effects of a single approach.[21] Further studies should consider these possible limitations and confirm the results related to physical and neuropsychological outcomes.

Authors' contributions

SS, GZ, AB, NB and GS conceptualized the protocol. AB, GM, GF drafted the manuscript; AB, GF, GM, NB, SS, and GS read and correct the manuscript. All authors have read and approved the final manuscript.

Funding statement

This research was supported by the Multiple Sclerosis Italian Society (Grant 2018/R/19).

Competing interests

The authors declare that they have no competing interests.

Figure 1 CONSORT flow diagram of the study

REFERENCES

1 Organization WH, Federation MSI. *Atlas : multiple sclerosis resources in the world 2008*. World Health Organization 2008. https://apps.who.int/iris/handle/10665/43968 (accessed 25 Mar 2021).

2 Khan F, Amatya B. Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. *Arch Phys Med Rehabil* 2017;**98**:353–67. doi:10.1016/j.apmr.2016.04.016

3 Cameron MH, Nilsagard Y. Balance, gait, and falls in multiple sclerosis. *Handb Clin Neurol* 2018;**159**:237–50. doi:10.1016/B978-0-444-63916-5.00015-X

4 Martin CL, Phillips BA, Kilpatrick TJ, *et al.* Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler Houndmills Basingstoke Engl* 2006;**12**:620–8. doi:10.1177/1352458506070658

5 Prosperini L, Sbardella E, Raz E, *et al.* Multiple sclerosis: white and gray matter damage associated with balance deficit detected at static posturography. *Radiology* 2013;**268**:181–9. doi:10.1148/radiol.13121695

6 Cameron MH, Lord S. Postural control in multiple sclerosis: implications for fall prevention. *Curr Neurol Neurosci Rep* 2010;**10**:407–12. doi:10.1007/s11910-010-0128-0

7 Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008;**7**:1139–51. doi:10.1016/S1474-4422(08)70259-X

8 Giazkoulidou A, Messinis L, Nasios G. Cognitive functions and social cognition in multiple sclerosis: An overview. *Hell J Nucl Med* 2019;**22 Suppl**:102–10.

9 Chalah MA, Ayache SS. Deficits in Social Cognition: An Unveiled Signature of Multiple Sclerosis. *J Int Neuropsychol Soc JINS* 2017;**23**:266–86. doi:10.1017/S1355617716001156

10 Saverino A, Waller D, Rantell K, *et al.* The Role of Cognitive Factors in Predicting Balance and Fall Risk in a Neuro-Rehabilitation Setting. *PloS One* 2016;**11**:e0153469. doi:10.1371/journal.pone.0153469

11 Negahban H, Mofateh R, Arastoo AA, *et al.* The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture* 2011;**34**:479–84. doi:10.1016/j.gaitpost.2011.06.023

12 Song J-H. The role of attention in motor control and learning. *Curr Opin Psychol* 2019;**29**:261–5. doi:10.1016/j.copsyc.2019.08.002

13 Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2015;**21**:123–31. doi:10.1177/1352458514547408

14 Chamard Witkowski L, Mallet M, Bélanger M, *et al.* Cognitive-Postural Interference in Multiple Sclerosis. *Front Neurol* 2019;**10**:913. doi:10.3389/fneur.2019.00913

15 Ruggieri S, Fanelli F, Castelli L, *et al.* Lesion symptom map of cognitive-postural interference in multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2018;**24**:653–62. doi:10.1177/1352458517701313

16 Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Interv Aging* 2017;**12**:557–77. doi:10.2147/CIA.S125201

17 Rooney S, Ozkul C, Paul L. Correlates of dual-task performance in people with multiple sclerosis: A systematic review. *Gait Posture* 2020;**81**:172–82. doi:10.1016/j.gaitpost.2020.07.069

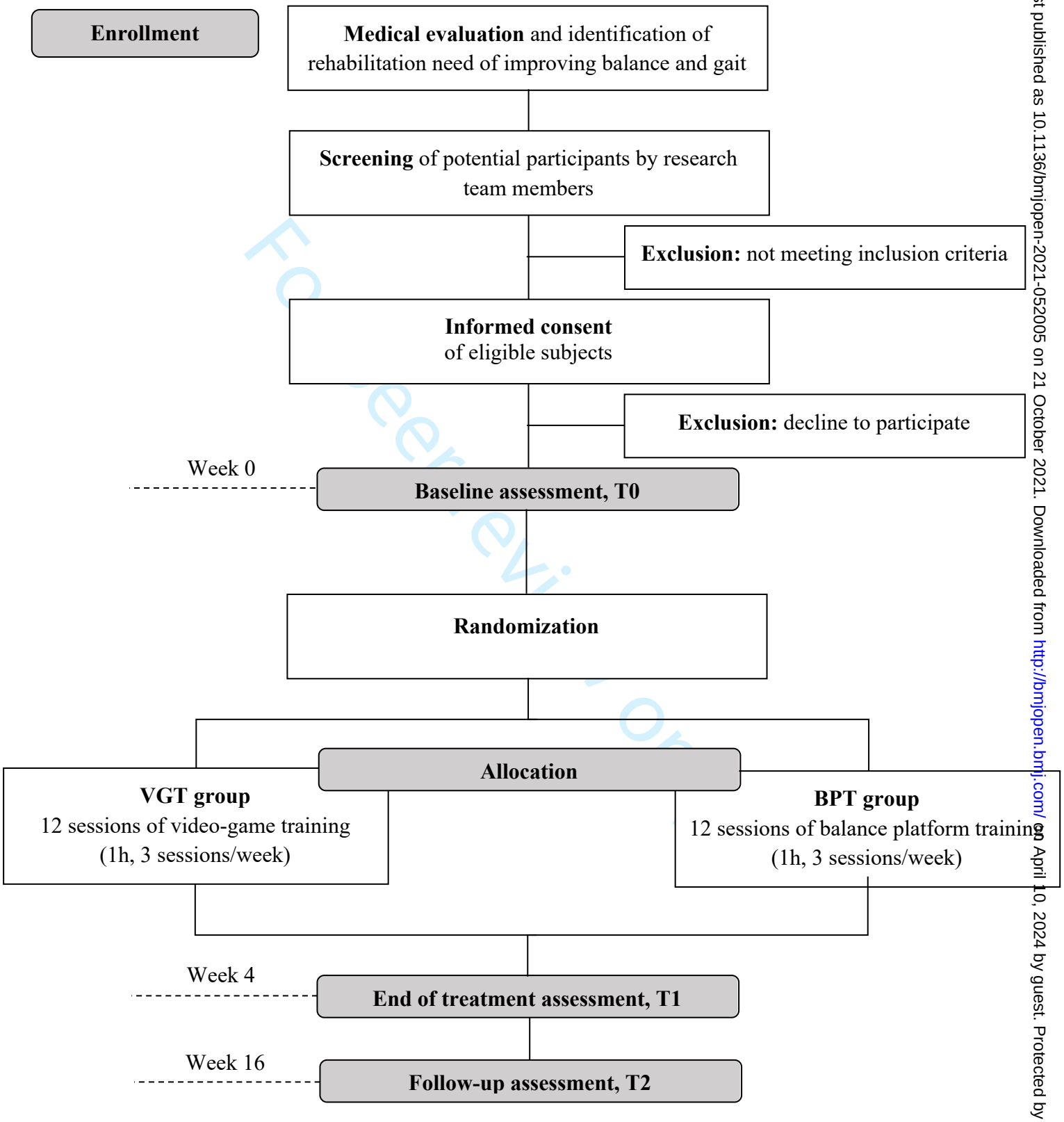
18 Mulder T, Zijlstra W, Geurts A. Assessment of motor recovery and decline. *Gait Posture* 2002;**16**:198–210. doi:10.1016/s0966-6362(01)00157-6

19 Laver KE, Lange B, George S, *et al.* Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev* 2017;**11**:CD008349. doi:10.1002/14651858.CD008349.pub4

20 Forsberg A, Nilsagård Y, Boström K. Perceptions of using videogames in rehabilitation: a dual perspective of people with multiple sclerosis and physiotherapists. *Disabil Rehabil*

2015;**37**:338–44. doi:10.3109/09638288.2014.918196
21 Maggio MG, Russo M, Cuzzola MF, *et al.* Virtual reality in multiple sclerosis rehabilitation: A review on cognitive and motor outcomes. *J Clin Neurosci Off J Neurosurg Soc Australas* 2019;**65**:106–11. doi:10.1016/j.jocn.2019.03.017
22 Parra-Moreno M, Rodríguez-Juan JJ, Ruiz-Cárdenas JD. Use of commercial video games to improve postural balance in patients with multiple sclerosis: A systematic review and meta-analysis of randomised controlled clinical trials. *Neurol Barc Spain* Published Online First: 7 March 2018. doi:10.1016/j.nrl.2017.12.001
23 Brichetto G, Spallarossa P, de Carvalho MLL, *et al.* The effect of Nintendo® Wii® on balance in people with multiple sclerosis: a pilot randomized control study. *Mult Scler Houndmills Basingstoke Engl* 2013;**19**:1219–21. doi:10.1177/1352458512472747
24 Pitteri M, Dapor C, Ziccardi S, *et al.* Visual-Attentional Load Unveils Slowed Processing Speed in Multiple Sclerosis Patients: A Pilot Study with a Tablet-Based Videogame. *Brain Sci* 2020;**10**. doi:10.3390/brainsci10110871
25 Bove R, Rowles W, Zhao C, *et al.* A novel in-home digital treatment to improve processing speed in people with multiple sclerosis: A pilot study. *Mult Scler Houndmills Basingstoke Engl* 2021;**27**:778–89. doi:10.1177/1352458520930371
26 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586. doi:10.1136/bmj.e7586
27 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**:1444–52. doi:10.1212/wnl.33.11.1444
28 Kalron A, Dolev M, Givon U. Further construct validity of the Timed Up-and-Go Test as a measure of ambulation in multiple sclerosis patients. *Eur J Phys Rehabil Med* 2017;**53**:841–7. doi:10.23736/S1973-9087.17.04599-3
29 Beatty WW, Goodkin DE. Screening for cognitive impairment in multiple sclerosis. An evaluation of the Mini-Mental State Examination. *Arch Neurol* 1990;**47**:297–301. doi:10.1001/archneur.1990.00530030069018
30 Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332. doi:10.1136/bmj.c332
31 Straudi S, Severini G, Sabbagh Charabati A, *et al.* The effects of video game therapy on balance and attention in chronic ambulatory traumatic brain injury: an exploratory study. *BMC Neurol* 2017;**17**:86. doi:10.1186/s12883-017-0871-9
32 Nilsagård YE, Forsberg AS, von Koch L. Balance exercise for persons with multiple sclerosis using Wii games: a randomised, controlled multi-centre study. *Mult Scler Houndmills Basingstoke Engl* 2013;**19**:209–16. doi:10.1177/1352458512450088
33 Bonnechère B, Jansen B, Omelina L, *et al.* The use of commercial video games in rehabilitation: a systematic review. *Int J Rehabil Res Int Z Rehabil Rev Int Rech Readaptation* 2016;**39**:277–90. doi:10.1097/MRR.0000000000000190
34 Cano Porras D, Siemonsma P, Inzelberg R, *et al.* Advantages of virtual reality in the rehabilitation of balance and gait: Systematic review. *Neurology* 2018;**90**:1017–25. doi:10.1212/WNL.0000000000005603
35 Eftekharsadat B, Babaei-Ghazani A, Mohammadzadeh M, *et al.* Effect of virtual reality-based balance training in multiple sclerosis. *Neurol Res* 2015;**37**:539–44. doi:10.1179/1743132815Y.0000000013
36 Mañago MM, Cameron M, Schenkman M. Association of the Dynamic Gait Index to fall history and muscle function in people with multiple sclerosis. *Disabil Rehabil* 2020;**42**:3707–12. doi:10.1080/09638288.2019.1607912
37 Wagner JM, Norris RA, Van Dillen LR, *et al.* Four Square Step Test in ambulant persons with multiple sclerosis: validity, reliability, and responsiveness. *Int J Rehabil Res Int Z Rehabil Rev Int Rech Readaptation* 2013;**36**:253–9. doi:10.1097/MRR.0b013e32835fd97f
38 Soke F, Eldemir S, Ozkan T, *et al.* The functional reach test in people with multiple

sclerosis: a reliability and validity study. *Physiother Theory Pract* 2021;:1–15. doi:10.1080/09593985.2021.1938308
39 Hobart J, Lamping D, Fitzpatrick R, *et al.* The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain J Neurol* 2001;**124**:962–73.
40 Marengo D, Rosato R, Gamberini G, *et al.* Examining the validity of the multiple-sclerosis walking scale-12 with Rasch analysis: Results from an Italian study. *Mult Scler Relat Disord* 2019;**36**:101400. doi:10.1016/j.msard.2019.101400
41 Rooney S, McFadyen DA, Wood DL, *et al.* Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis. *Mult Scler Relat Disord* 2019;**35**:158–63. doi:10.1016/j.msard.2019.07.028
42 Coghe G, Corona F, Marongiu E, *et al.* Fatigue, as measured using the Modified Fatigue Impact Scale, is a predictor of processing speed improvement induced by exercise in patients with multiple sclerosis: data from a randomized controlled trial. *J Neurol* 2018;**265**:1328–33. doi:10.1007/s00415-018-8836-5
43 Sacco R, Santangelo G, Stamenova S, *et al.* Psychometric properties and validity of Beck Depression Inventory II in multiple sclerosis. *Eur J Neurol* 2016;**23**:744–50. doi:10.1111/ene.12932
44 Santangelo G, Sacco R, Siciliano M, *et al.* Anxiety in Multiple Sclerosis: psychometric properties of the State-Trait Anxiety Inventory. *Acta Neurol Scand* 2016;**134**:458–66. doi:10.1111/ane.12564
45 Zimmermann P, Fimm B. A test battery for attentional performance. In: *Applied Neuropsychology of Attention. Theory, Diagnosis and Rehabilitation*. 2002. 110–51.
46 Coghe G, Pilloni G, Zucca E, *et al.* Exploring cognitive motor interference in multiple sclerosis by the visual Stroop test. *Mult Scler Relat Disord* 2018;**22**:8–11. doi:10.1016/j.msard.2018.02.026
47 Benedict RH, DeLuca J, Phillips G, *et al.* Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2017;**23**:721–33. doi:10.1177/1352458517690821
48 Sun R, Moon Y, McGinnis RS, *et al.* Assessment of Postural Sway in Individuals with Multiple Sclerosis Using a Novel Wearable Inertial Sensor. *Digit Biomark* 2018;**2**:1–10. doi:10.1159/000485958
49 Severini G, Straudi S, Pavarelli C, *et al.* Use of Nintendo Wii Balance Board for posturographic analysis of Multiple Sclerosis patients with minimal balance impairment. *J Neuroengineering Rehabil* 2017;**14**:19. doi:10.1186/s12984-017-0230-5
50 Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. New York: : Routledge 1988. doi:10.4324/9780203771587
51 Dalmazane M, Gallou-Guyot M, Compagnat M, *et al.* Effects on gait and balance of home-based active video game interventions in persons with multiple sclerosis: A systematic review. *Mult Scler Relat Disord* 2021;**51**:102928. doi:10.1016/j.msard.2021.102928
52 Casuso-Holgado MJ, Martín-Valero R, Carazo AF, *et al.* Effectiveness of virtual reality training for balance and gait rehabilitation in people with multiple sclerosis: a systematic review and meta-analysis. *Clin Rehabil* 2018;**32**:1220–34. doi:10.1177/0269215518768084
53 Nascimento AS, Fagundes CV, Mendes FADS, *et al.* Effectiveness of Virtual Reality Rehabilitation in Persons with Multiple Sclerosis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Mult Scler Relat Disord* 2021;**54**:103128. doi:10.1016/j.msard.2021.103128
54 Sokolov AA, Grivaz P, Bove R. Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. *Curr Treat Options Neurol* 2018;**20**:53. doi:10.1007/s11940-018-0538-x
55 Mura G, Carta MG, Sancassiani F, *et al.* Active exergames to improve cognitive functioning in neurological disabilities: a systematic review and meta-analysis. *Eur J Phys Rehabil Med* 2018;**54**:450–62. doi:10.23736/S1973-9087.17.04680-9



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Università degli Studi di Ferrara

ARCISPEDALE S. ANNA
DIPARTIMENTO DI NEUROSCIENZE/RIABILITAZIONE

Foglio informativo per il paziente

Gentile Signora/e,
Lei è invitata/o a partecipare ad uno studio che viene effettuato presso questo ospedale cui lei si è rivolto per motivi di diagnosi o cura. Si prenda tutto il tempo necessario per leggere questo foglio. Se qualcosa non le è chiaro, non esiti a porre tutte le domande che vorrà.

Il titolo dello studio è:

Il ruolo della video game terapia sull'equilibrio e le funzioni cognitive in pazienti con sclerosi multipla e disabilità lieve o moderata. Uno studio pilota randomizzato controllato.

Perché questo studio clinico viene proposto?
Spesso la Sclerosi Multipla si caratterizza per la presenza sia di disordini dell'equilibrio, sia di disordini cognitivi, cioè quelle funzioni del cervello quali l'attenzione e la memoria. Gli aspetti cognitivi non devono essere considerati come una dimensione separata dagli aspetti motori, ad esempio l'attenzione agisce sul controllo dell'equilibrio. Inoltre, nella vita quotidiana è possibile osservare la compresenza dei due aspetti: basti pensare a quando si cammina e contemporaneamente si parla. Il trattamento riabilitativo dovrebbe quindi tenere conto di entrambi questi aspetti, proponendo attività che potenzino la performance sia cognitiva che motoria. La Video-Game Terapia potrebbe essere uno strumento utile in tal senso, in quanto può favorire il trattamento sia dell'equilibrio sia degli aspetti cognitivi contemporaneamente. Inoltre, rispetto a trattamenti più "classici", la Video-game Terapia aumenta la motivazione, favorendo l'acquisizione di nuove competenze. E' inoltre meno dispendiosa e più "versatile" in quanto è possibile proseguire il trattamento riabilitativo anche al domicilio. Con questo studio esplorativo vogliamo confrontarne gli effetti rispetto ai trattamenti "classici" per l'equilibrio, sia per quanto riguarda il miglioramento dell'equilibrio, sia delle funzioni cognitive in generale.

Lo scopo principale di questo studio è quello di verificare gli effetti di un terapia mediante un dispositivo commercialmente disponibile sull'equilibrio e sulle funzioni cognitive nei pazienti SM deambulanti rispetto a un trattamento riabilitativo "standard". In secondo luogo, esploreremo gli effetti in altri settori che sono generalmente compromessi nella popolazione MS e che possono essere migliorati mediante riabilitazione motoria, come il benessere psicologico, la stanchezza e la qualità di vita.

Quali sono le caratteristiche di questo studio?
Lo studio prevede di raccogliere dati di sicurezza ed efficacia di una procedura confrontata con quella attualmente in uso secondo le norme di buona pratica clinica.
Verrà reclutato un campione di pazienti con Sclerosi Multipla presso l'Azienda Ospedaliero - Universitaria di Ferrara. I soggetti reclutati saranno attribuiti in maniera casuale in gruppi che riceveranno la Video Game Terapia (VGT) o la Terapia mediante Piattaforma dell'Equilibrio (BPT).
Il gruppo sperimentale riceverà 12 sessioni di allenamento VGT (3 volte alla settimana) per 4 settimane. Il gruppo di controllo riceverà la stessa quantità di sessioni BPT. Selezioneremo le misure di equilibrio che esplorano un'ampia gamma di compiti motori. Saranno inoltre somministrati test per valutare l'affaticamento, le funzioni cognitive e il benessere fisico e psicologico. L'equilibrio verrà valutato mediante una serie di test

clinici funzionali che indagano un'ampio spettro di compiti motori. Inoltre verrà eseguito un esame della postura attraverso una pedana in grado di misurare le oscillazioni corporee in posizione eretta. Verranno somministrati questionari per valutare la fatica, il benessere psicofisico e la qualità di vita. Le misure verranno raccolte prima del trattamento (T0), alla fine (T1) e a distanza di 3 mesi (T2) per valutare il mantenimento dei risultati.

Chi propone lo studio?
Lo Studio è proposto dal Settore di Medicina Riabilitativa "S. Giorgio" – Dipartimento di Neuroscienze/Riabilitazione dell'Azienda Ospedaliero-Universitaria di Ferrara.

Perché sono invitato a partecipare allo studio?
Le stiamo proponendo di partecipare a questo studio perché è affetto da Sclerosi Multipla
E' previsto che partecipino a questo studio 48 pazienti.

Cosa comporta la partecipazione allo studio, rispetto al normale percorso diagnostico-terapeutico per la mia malattia?
Lo studio prevede la creazione di due gruppi di pazienti: il primo gruppo riceverà la Video-Game Terapia, mentre il secondo gruppo riceverà un trattamento mediante Piattaforma dell'Equilibrio. L'attribuzione ad un gruppo o ad un altro è casuale. Prima dell'inizio del trattamento, alla fine del trattamento e a distanza di tre mesi, verranno effettuate misurazioni attraverso specifici test, così da permettere un confronto tra i due gruppi.

Quali rischi o inconvenienti potrei avere dalla partecipazione a questo studio?
Non vi sono rischi legati allo studio.
Eventuali nuove informazioni che potrebbero influenzare la sua volontà di partecipazione le verranno comunicate il più presto possibile. Lo stesso vale per una eventuale interruzione o sospensione dello studio.

Quali vantaggi potrei avere nel partecipare a questo studio?
Lei potrebbe non avere beneficio diretto dalla partecipazione. Questo studio potrà contribuire a migliorare la diagnosi e la comprensione della sua malattia, e portare allo sviluppo di nuovi trattamenti riabilitativi per i disturbi dell'equilibrio e cognitivi. I risultati dello studio saranno poi pubblicati su riviste scientifiche nazionali o internazionali. Per la partecipazione allo studio non è previsto alcun compenso.

Sono obbligato a partecipare allo studio?
No. La decisione di partecipare è assolutamente libera. Se lei acconsente ha la possibilità di contribuire alla ricerca medica attraverso questo studio. Se però non vuole partecipare, non deve fornire alcuna spiegazione. Il suo rifiuto non influenzerà in alcun modo il trattamento che le verrà proposto, e riceverà comunque tutte le terapie previste dalla buona pratica clinica per la sua patologia.

Potrò cambiare idea dopo aver accettato di partecipare?
Sì. La decisione di partecipare allo studio è volontaria e libera, e lei ha il diritto di revocare il suo consenso in qualunque momento lo desideri, senza fornire spiegazioni e senza che questo influenzi in alcun modo il trattamento che le verrà proposto, che sarà comunque il migliore disponibile.

Se partecipo allo studio, miei dati personali e clinici saranno noti a tutti?
No. I suoi dati clinici saranno resi anonimi. Il suo nome e cognome saranno sostituiti da un codice che solo il responsabile dello studio conoscerà.

Trattamento dei dati
Se Lei deciderà di partecipare allo studio, tutti i dati raccolti (età, sesso, origine etnica e i dati clinici), saranno archiviati elettronicamente in maniera rigorosamente anonima, ai sensi del Decreto Legislativo n. 196/03 sulla tutela delle persone rispetto al trattamento dei dati personali e saranno trattati in modo assolutamente riservato. I dati verranno conservati presso l'unità Operativa di Medicina Riabilitativa S.

Giorgio dell'Azienda Ospedaliero-Universitaria di Ferrara per un periodo di 2 anni dalla chiusura dello studio. La persona responsabile della gestione dei suoi dati per questo studio e reparto è la dr.ssa Sofia Straudi.
L'accesso diretto alla sua documentazione sarà consentito a tutti coloro che sono coinvolti nell'effettuazione dello studio (personale sanitario, personale che elabora i dati, personale ispettivo e quant'altri abilitati dal protocollo di studio e/o dalle normative vigenti) e alle autorità regolatorie nella misura permessa dalle leggi senza violare la sua riservatezza.

Il medico della ricerca le consegnerà una lettera rivolta al suo medico di base, per informarlo della sua partecipazione allo studio, per la migliore conduzione clinica dello stesso.

Chi ha approvato lo studio?
Il protocollo dello studio è stato redatto in accordo con la dichiarazione di Helsinki sull'etica della ricerca in medicina ed è stato approvato dal Comitato Etico di questo ospedale.
Se Lei accetterà di partecipare a questo studio Le verrà chiesto di **firmare e datare** di suo pugno questo foglio informativo di cui Le sarà consegnata copia assieme alla copia del foglio di consenso.

A chi posso rivolgermi se ho dei problemi durante lo studio?
Il medico referente per questo studio è la Dr.ssa Sofia Straudi Tel. 0532-236185 (s.straudi@ospfe.it)
Lo staff operativo coinvolto nello studio è costituito dai seguenti operatori:
1) Andrea Baroni (a.baroni@ospfe.it)
2) Nino Basaglia
3) Anna Scotti
4) Giada Milani
5) Giulia Fregna

Nome in stampatello del partecipante allo studio

_____

Data e Firma

_____

Nome in stampatello del Medico ricercatore

_____

Data e Firma

Il ruolo della video game terapia sull'equilibrio e le funzioni cognitive in pazienti con sclerosi multipla e disabilità lieve o moderata. Uno studio pilota randomizzato controllato.

Modulo di consenso allo studio e al trattamento dei dati

Questo modulo deve essere firmato da Lei solo nel caso decida di partecipare allo studio. E' importante che Lei abbia discusso approfonditamente con il Medico prima di firmare questo consenso, anche sulla base del foglio informativo a cui esso si riferisce. Partecipano allo studio solo i Pazienti che accettano. Il Paziente può ritirare il suo consenso in ogni momento.

Dichiaro di ricevere copia firmata del presente modulo di consenso unitamente a copia datata e firmata del foglio informativo. Dichiaro inoltre di:

- aver ricevuto dal medico esaurienti spiegazioni in merito alla richiesta di partecipazione allo studio, in particolare sulle finalità e sulle procedure;
- aver letto e compreso il foglio informativo che mi è stato consegnato con sufficiente anticipo e che conferma quanto mi è stato spiegato a voce;
- aver avuto la possibilità di porre domande ed aver avuto risposte soddisfacenti;
- farmi carico della consegna della lettera relativa allo studio per il mio medico di famiglia;
- essere consapevole che la partecipazione è volontaria, con l'assicurazione che il rifiuto a partecipare non influirà sulla scelta della terapia migliore per me;
- essere consapevole che, se ritirerò il mio consenso, i dati raccolti prima del ritiro del consenso saranno utilizzati dal ricercatore;
- autorizzare il trattamento dei miei dati personali ai sensi del Decreto legislativo n. 196/2003 (codice privacy) con le finalità indicate nello studio
- Acconsento a partecipare allo studio clinico suddetto

Nome in stampatello del partecipante allo studio

_____

Luogo e Data nascita_____

Residenza:

Data e Firma

_____

Nome in stampatello del Medico ricercatore

_____

Data e Firma

_____

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**1, 3**
	2b	All items from the World Health Organization Trial Registration Data Set	**-**
Protocol version	3	Date and version identifier	**8**
Funding	4	Sources and types of financial, material, and other support	**8**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 2, 8**
	5b	Name and contact information for the trial sponsor	**1**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**8**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**7, 8**

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

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**7**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**2**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**3**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**3**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**3**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**3**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**3**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**5**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**4**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**7**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**7**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**7**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**7**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**7**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**7**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**4, 7**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**7**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**3**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**-**

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**2, 3**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**not applicable**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**3**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**8**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**-**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**not applicable**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**8**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**not present**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**not present**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**sent to editorial office_**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**not applicable**

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

BMJ Open

Video game therapy on mobility and dual tasking in multiple sclerosis. Study protocol for a randomized controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052005.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Sep-2021
Complete List of Authors:	Baroni, Andrea; Ferrara University Hospital, Department of Neuroscience and Rehabilitation Fregna, Giulia; Ferrara University Hospital, Department of Neuroscience and Rehabilitation Milani, Giada; University of Ferrara, Doctoral Program in Translational Neurosciences and Neurotechnologies Severini, G; University College Dublin, School of Electrical and Electronic Engineering Zani, Giulia; Ferrara University Hospital, Department of Neuroscience and Rehabilitation Basaglia, Nino; University of Ferrara, Department of Neuroscience and Rehabilitation Straudi, Sofia; University of Ferrara, Department of Neuroscience and Rehabilitation
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, REHABILITATION MEDICINE, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Video game therapy on mobility and dual tasking in multiple sclerosis. Study protocol for a randomized controlled trial.

Andrea Baroni[1], PhD, Giulia Fregna[1], MS, Giada Milani[1,2], MS, Giacomo Severini[3], PhD, Giulia Zani[1], MS, Nino Basaglia[1], MD, Sofia Straudi[1,4], MD, PhD

Affiliations:

[1] Department of Neuroscience and Rehabilitation, Ferrara University Hospital, Ferrara, Italy

[2] Ferrara University, Doctoral Program in Translational Neurosciences and Neurotechnologies, Ferrara, Italy

[3] School of Electrical and Electronic Engineering, University College Dublin, Dublin, Ireland

[4] Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy

Correspondence

Dr. Sofia Straudi, MD, PhD. Neuroscience and Rehabilitation Department, Ferrara University Hospital. Via Aldo Moro 8, 44124 Cona, Ferrara, Italy. s.straudi@ospfe.it 0039 0532236953

ABSTRACT

Introduction Multiple Sclerosis (MS) is one of the major causes of disability in young adults and affects mobility, compromising daily living activities and participation in social life. Cognitive domain is also frequently impaired in people with MS (PwMS), particularly the capacity to perform dual-task activities. Impaired cognitive processing abilities need to be treated, and motor and cognitive aspects need to be considered together. Recently, video game therapy (VGT) has been used in rehabilitation to improve motor outcomes and cognitive processing speed. The aim of this study is to test the efficacy of commercially available VGT on mobility and dual tasking in PwMS compared to standardized balance platform training (BPT).

Methods and analysis This will be a parallel-assignment, double-blinded randomized control trial. Forty-eight (24 per arm) PwMS (EDSS 4-5.5) will be randomly assigned to receive 1-h training session over four weeks (three sessions/week) of either: (1) VGT on commercial video game console to train balance and mobility-related activities or (2) BPT to perform balance, postural stability and weight-shifting exercises with and without visual feedback. The same assessor will evaluate outcome measures at points: before and after the twelve training sessions and at three months of follow-up. The primary outcome will be functional mobility, assessed by the Timed Up and Go (TUG) test. We will also evaluate gait, risk of fall, fatigue and health-related quality of life as well as cognitive and psychological aspects (depression, anxiety and attentional performance) and stability through posturographic evaluation. Dual-tasking assessment will be performed combining posturographic and neuropsychological tests. Data analysis will be performed to compare the efficacy of the two treatments.

Ethics and dissemination Ethical approval have been granted from the local Ethics Committee. Study results will be communicated through high-quality journals and national and international conferences.

Trial registration ClinicalTrials.gov, Identifier: NCT03353974

Keywords Multiple sclerosis, video game, mobility, balance, dual-task

Strengths and limitations of this study

- This trial will use objective evaluation as a posturographic assessment to test balance and dual-task.
- Motor and cognitive outcomes will be assessed separately and in association.
- Results from this trial will need a larger sample to be confirmed.
- This study protocol includes only young subjects (aged under 60) with good comprehensive functioning.
- This study does not analyze long-term effects (over three months).

INTRODUCTION

Multiple Sclerosis (MS) is characterized by multifocal inflammatory demyelinated plaques distributed over time and space within the Central Nervous System (CNS). It affects approximately 1.3 million people worldwide and is a major cause of chronic neurological disability in young adults aged 18–50 years.[1,2] Deficits in balance control and cognition are prevalent impairments in people with MS (PwMS) [3], even at an early stage and without clinical disability.[4] Previous studies have reported that 30 to 63% of PwMS experience a fall event between 1 and 12 months since the onset of the disease.[5] Balance maintenance is a complex task that depends on the continuous flow of proprioceptive information from the muscles, tendons, joints, skin, vestibular and visual systems toward the CNS.[3] In PwMS, the extended damage caused in the CNS leads to a decreased ability in integrating the afferent proprioceptive information, thus negatively influencing postural response and the capability to maintain balance safely.[5,6] Balance impairment can consistently limit the activities of daily living and the active participation in social life.

Cognitive impairment is various among PwMS, with current prevalence rates ranging from 43% to 70%.[7] The following cognitive domains are frequently impaired: memory processing speed, attention/concentration, and executive functioning.[8] Cognitive impairments are associated with reduced functional status in MS. They have a deleterious impact on the individual's personal, occupational, and social functioning and the comprehensive quality of life.[9]

The role of cognitive functioning on motor performance and balance control is widely known.[10] However, the effects of impaired cognitive processes on balance efficacy have not been extensively investigated in PwMS.[11] Besides, the comprehensive link between attention and motor-action has been supported by several studies.[12] Selective attention allows the execution of a correct motor response by selecting relevant information between the task and the distractors, and it is essential for action planning. Concerning the cognitive-motor interference (CMI), this relation is directly measurable by the dual-task cost (DTC) [13,14], investigated in PwMS through the Stroop Test.[15] Dual-task performance is the capacity to do two tasks simultaneously, particularly motor and cognitive tasks. The subject's attention is drawn to an external source of attention while the primary task is ongoing, resulting in cognitive-motor interactions.[16] Concerning the constrained action hypothesis, this attentional change may lead motor systems to react automatically, thus increasing the performance effectiveness.[17] The processing capacity required for doing dual-task activities may be affected by cognitive impairments.[18] In subjects with neurological disorders, such as PwMS, the ability of doing a motor task simultaneously to a cognitive one is frequently affected. [17]

It is plausible that motor deficits enhance the cognitive demands necessary to execute functional movements, and the concurrent performance of tasks may exceed cognitive processing abilities.[19] Considering the strong impact of dual tasking on activities of daily living (ADL) [7], rehabilitative treatment does not have to consider the motor and cognitive aspects separately.

In recent years, active video games technologies have begun to be used as a treatment tool in rehabilitation given their low-cost, high portability, off-the-shelf nature, and ability to deliver engaging, high-repetitive, task-oriented, standardized, active learning therapies.[20] Moreover, PwMS defined gaming experience as fun, challenging, and self-motivating, critical elements for successful motor learning.[21] Active video games' multisensory feedback provided to patients may potentiate the use-dependent plasticity processes in the sensorimotor cortex, promoting functional recovery.[22] Furthermore, combined training of cognitive and motor abilities in constantly changing virtual environments is particularly suited to address dual-tasking as required for the constantly changing situations of everyday life.[23]

The evidence of interactive video game therapeutic exercises for improving balance and motor functions in PwMS were inconclusive, even if few studies showed a possible positive effect on balance and cognitive functions such as processing speed.[24–27] Furthermore, patients' motivation seems to be capable of being increased during active video game rehabilitation, allowing patients to exercise more consistently.[22]

All previous studies did not investigate the effects on motor and cognitive functions simultaneously, particularly when compared to conventional instrumental balance training.

Aims

This study aims to test the efficacy of a commercially available VGT (Xbox Kinect) on mobility and dual-tasking in ambulatory PwMS in comparison to a standardized balance platform training (BPT). We hypothesize that augmented feedback during VGT, in terms of intensity and type, would activate the cognitive components of motor learning more effectively than BPT. Moreover, a challenging and engaging approach contributes to enhance treatment adherence and patient's satisfaction.

METHODS AND ANALYSIS

Study design and setting

This is a parallel-assignment, double-blinded randomized control trial. The outcome assessor and the data analyst will be blinded to the group allocation of participants. PwMS who meet the inclusion criteria and provide written informed consent will be assigned to two treatments, the Video game Therapy (VGT) or the Balance Platform Training (BPT). The trial protocol has been registered on ClinicalTrials.gov (NCT03353974).

The protocol of this clinical trial is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[28] A SPIRIT Checklist is available as an additional file (Additional file 1). Subjects will be recruited from the patients afferent to Outpatient Rehabilitation Clinic at University Hospital of Ferrara. Patients' recruitment started on 1st December 2017, and it's going to finish on 1st October 2022.

Selection criteria and recruitment of participants

People affected by MS will be included if they meet the following inclusion criteria:

- Men and women, aged 18 to 60 years;
- Diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding three months;
- Disability rate defined by EDSS score from 4 to 5.5 [29];
- Balance impairments with increased fall risk, defined as TUG > 8.4s [30];
- Mini Mental Status Examination (MMSE) score ≥24/30.[31]

Exclusion criteria will be:

- Other (neurological) conditions that may affect motor function;
- Visual impairments (daltonism and visual acuity deficit);
- Medical conditions might interfere with the ability to complete the study protocol safely.

During the first appointment, potential participants will be informed about all the study procedures and screened following the inclusion criteria. Suppose they meet inclusion criteria and are interested in taking part in the study. In that case, the physician will give them a letter explaining study purpose and procedures, time commitments, risks, potential benefits, treatment alternatives, study staff contact information and the Consent Form. A copy of the Consent Form is available as an additional file (Additional file 2). In the following three days, the potential participant will be contacted and asked about its decision; if the subject decides to take part in the study, the research staff will give him/her an appointment for the consign to the signed Consent Form and for the baseline outcome measures, conducted by a physiotherapist. If the subject rejects participation in the study, the research staff remains available for further information. The total number of subjects screened for participation and

the number of subjects who decline to participate will be recorded, according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1).[32]

Randomization and blinding

People meeting inclusion criteria who decided to participate will be assigned to one of the two treatment groups through a block randomization approach (1:1 ratio). The randomization scheme will be set up in permuted blocks of 4 to ensure a similar number of participants between groups. The randomization scheme will be generated using the website Randomization.com (http://www.randomization.com) and managed by an external administrator to the research group to prevent selection bias. The outcome assessor will be blinded about the subject's group allocation. All outcome data and assignment groups will be organised in different datasets to maintain the blinding during data analysis. The privacy of the participants and their medical records will be guaranteed by treating the data according to the Italian Law n. 196/2003, to the "Safe Harbor Act" (2000/520/CE) and to the "European Union Data Protection Directive (95/46/EC 24 October 1995)."

Intervention

All participants will receive twelve 1-h training sessions over four weeks, resulting in a three sessions/week scheme. To manage possible absence lasting one or more treatment sessions, a potential window of 5 weeks will be set to ensure the achievement of all 12 sessions. Subjects who miss a training session will be contacted by phone to determine the absence's reasons and maintain adherence to following treatment sessions. Subjects who miss more than three consecutive treatment sessions will be excluded from the study.

Every training session consists of about fifty minutes of exercise and about ten minutes of mobility and flexibility activity to prevent muscle soreness due to movement. All interventions will be delivered at the Rehabilitation Clinic of the University Hospital of Ferrara.

Video game Therapy (VGT)

VGT will be delivered with a commercial video game console, Kinect for Xbox 360 game system (Microsoft Corporation, Redmond, Washington, USA). Pre-selected games were chosen from "Kinect Adventures!" and "Kinect Sports" (Microsoft Game Studios, Redmond, Washington, USA) that encompassed a wide range of motor activities in a standing position. Specifically, balance and mobility-related motor tasks were trained, such as sidestepping, lateral weight shifting, jumping, walking (lateral, forward and backward), and arm goal reaching.

Kinect is a commercial device therefore calibration of the instrument on the individual patient is not provided. The physiotherapy treatment with this device will be set by the physiotherapist basing on clinical observations of the patient's characteristics, preferences and level of functioning.

A list of games will be tested according to the patient's abilities and preferences. In the following sessions, games will be proposed with a randomized practice approach. Progression proceeds over time according to the patients' motor and balance improvements. Each task will consist of 2–5 minutes of training and a rest period will be given if necessary. During sessions, the patients will be carefully supervised by a physiotherapist who monitored the patient's safety (e.g., risk of falls, impulsive reactions). The physiotherapist will also give performance feedback and those provided by VGT: visual and augmented (knowledge of both results and performance).[33] Despite variability among treatment protocols available in the literature, our treatment dosage in terms of number of sessions and intervention duration is in line with other studies on the efficacy of exergame in people with neurological disorders.[25,34–36]

Balance Platform Therapy (BPT)

Balance/rebalancing, postural stability and weight-shifting exercises with and without visual feedback will be administered using a Balance Platform (Biodex Medical Systems, Shirley, New York, USA) that had been previously tested in MS patients.[37] Each task will be trained for about

2-3 minutes, followed by a rest period when necessary. During the first session, the tasks will be set to an "entry-level". The exercise progression will be adjusted over time according to the patient's capabilities (intermediate and difficult level). BPT offers visual feedback about reaching goals (augmented feedback). The physiotherapist will carefully supervise the patient and monitor his safety, providing additional external feedback during the activities.

Concomitant care and recommendations

All the subjects will be advised to not undertake other physical treatments until the end of the assessment period. Subjects will also be encouraged to not use the video game console at home for leisure to prevent confounding effects. It will be asked to patients to wear the same shoes and orthosis during all the outcome assessment and training sessions.

Intervention fidelity and monitoring of adverse events

All the interventions will be delivered by a physiotherapist with at least five years of experience in the treatment of PwMS, properly formed about VGT or BPT. Training sessions features and comments will be tracked in a precompiled form. Any unpredictable adverse events will be recorded in the patient's registry and the electronic study database. Their management will agree with the related hospital policies, with a referral for appropriate medical follow-up.

Outcome assessment and data collection

All the clinical evaluations will be performed at the Ferrara University Hospital by the same blinded assessor at the three time-point evaluations: (T0) baseline, before the first intervention; (T1) end of treatment, after the twelve therapy sessions; (T2) follow up, three months after the end of treatment. Clinical and posturographic assessment will be delivered by a physiotherapist trained adequately about evaluation procedures. A neuropsychologist with years of experience in the assessment and treatment of PwMS will provide cognitive tests. A physician member of the research team will define the patient's EDSS score. A team member will record the general demographic information (age, gender), comorbidities, and medical history of every participant. A summary of the study plan is reported in Table 1.

Table 1 Schedule of enrollment, interventions and assessments

	Study period				
	Enrollment	Allocation	Post allocation		Close-out
Time-point	T-1		T0	T1	T2
Enrollment					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Interventions					
Video game therapy			◆—	—◆	
Balance platform therapy			◆—	—◆	
Assessments					
Primary outcome					
Timed Up and Go test			X	X	X
Secondary outcome					
Clinical measures and questionnaires			X	X	X
Cognitive and psychological assessment			X	X	X
Posturographic assessment			X	X	X

Abbreviations: T-1 enrollment, T0 before treatment, T1 after treatment, T2 3-month follow-up

Primary outcome: Functional mobility

This function will be assessed by the Timed Up and Go (TUG) test, a reliable and valid performance-based measure of functional mobility.[30] The patient will be instructed to stand up from a chair, walk for three meters, cross a line marked on the floor, turn around, walk back and sit down. The time used to complete the task is recorded using a chronometer. During the assessment, the subject can use any necessary gait aid (not physical assistance). This test will be the first performed during the assessment session to reduce variability due to the subject's fatigue. The TUG test will be repeated three times, and the mean value will be recorded.

Secondary outcome measures

Secondary outcomes will include: (1) clinical measures and questionnaires, (2) cognitive and psychological assessment, (3) posturographic assessment. All secondary outcome measures will be carried out in random order.

Clinical measures and questionnaires:

a. Dynamic Gait Index (DGI): gait, balance and risk of fall are measured using DGI. DGI will evaluate not only usual steady-state walking but also during a more challenging task (i.e. cross obstacles, slalom). The subject will perform eight functional walking tests and score out of three (maximum total score is 24).[38]
b. Four Square Step Test (FSST): this timed test is intended to challenge the rapid change in direction while stepping forward, backward and sideways over a low obstacle. The faster the time measured to perform the task signifies a superior level of dynamic balance abilities. The minimal detectable change estimate for the FSST in MS is 4.6 s, and it was found to be a valid assessment tool in MS.[39]
c. Functional Reach Test (FRT): this test assesses the subject's stability by measuring the maximum distance an individual can reach forward while standing in a fixed position. A longer reaching distance indicates better postural control.[40]
d. Multiple Sclerosis Impact Scale – 29 (MSIS-29): this health-rated quality of life questionnaire assesses the impact of MS on physical and psychological functions. It is formed by 29 items on ADL I and II: 20 about physical activity and nine about psychological status. Each item can be scored with a value from 0 to 5; the total score is given by the sum of all the items and then is transformed in a range from 0 to 100.[41]
e. Multiple Sclerosis Walking Scale – 12 (MSWS-12): this questionnaire assesses the impact of MS on walking ability. It is formed by 12 items, asking the patient about his perception on gait speed, running, confidence ascending/descending stairs, balance and fatigue. The total score is obtained by the sum of the score of each item (0-5) and then transformed into a value from 0 to 100.[42]
f. Modified Fatigue Impact Scale (MFIS): this 21-item questionnaire assesses the perceived impact of fatigue on the subscale physical, cognitive, and psychological functioning during the past four weeks. MFIS has been recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines.[43,44]

Cognitive and psychological assessment

a. Beck Depression Inventory – Second Edition (BDI-II): this is a 21 item self-report measure that quantifies the severity of depression and over behavioural characteristics of depression.[45]

b. State Trait Anxiety Inventory (STAI-Y): this self-report questionnaire measures the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious. There are two subscales: 20 items allocated to each of the State Anxiety (S-Anxiety) and Trait Anxiety (T-Anxiety).[46]
c. Test of Attentional Performance (T.A.P. version 2.3): attentional performance will be evaluated using a neuropsychological computer test. Errors, omissions, and reaction times (RTs) will be recorded as outcomes of performance. Three modules of the T.A.P will be administered: Go-No Go subtest as it allows assessment of the specific ability of subjects to suppress undesired responses; alertness subtest that measures the simple reaction time in response to a visual stimulus and, divided attention subtest, that explored with "dual-task" test the ability to attend simultaneously two stimuli (visual and acoustic) processed in parallel.[47]
d. Stroop Color-Word Test (SCWT): this neuropsychological test is used to assess the ability to inhibit cognitive interference when processing a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute. Subjects are required to read three different tables as fast as possible. Two of them represent the "congruous condition", in which participants are required to read names of colours printed in black ink and name different colour patches. Conversely, the third table represents the incongruent condition, in which participants are required to name the colour of the ink instead of reading the word.[48]
e. Symbol Digit Modalities Test (SDMT): this neuropsychological test quantifies cognitive processing speed. It consists of orally report the correct number corresponding to a symbol in a pseudorandom sequence of nine symbols as quickly as possible.[49]

Posturographic assessment

Instrumented basic balance evaluation (IBBE): Force platform measurements are routinely used as objective markers of subjects' balance ability.[50,51] Several parameters can be extracted from the force platforms that correlate with balance ability and risk of falls in PwMS. During the instrumented tasks, subjects will be asked to stand on a force plate (BERTEC Model 4080–10, BERTEC, Columbus, Ohio, USA) with arms parallel to their body. Each subject will undergo five repetitions (each lasting 60 seconds) of two tasks that will consist in standing with the eyes open and standing with the eyes closed. The movements of the Center of Pressure (CoP) of the subjects will be recorded. A series of features will be extracted from the CoP traces to inform on different balance characteristics of each patient and the specific effect of each of the proposed therapies. Features that will be analyzed include different measures of CoP displacement in the anteroposterior (AP) and mediolateral (ML) directions, the CoP path length (total, AP and ML) and the CoP average and maximum speed.[33]
Dual-tasking assessment will be performed combining posturographic and neuropsychological tests: subjects will be asked to complete SCWT standing on the force platform, ensuring a similar condition to single-task SCWT. Head position will be fixed using a large panel fixed on the wall facing the force plate in order to prevent subjects lowering their head and distort the data. The ability to inhibit cognitive interferences during quiet and standing conditions will be compared.

Data management

Data analysis will be performed according to the research hypothesis mentioned. Stata Statistical Software (Release 13.1. College Station, TX: StataCorp LP, USA) will be used for data analysis

Sample size and power

The primary outcome of this study is to highlight differences in the time used to perform the TUG test between PwMS who underwent VGT and BPT. Our preliminary results from an unpublished pilot study (n=6) shown a VGT effect size of 0.93 in people with MS and EDSS < 6. Given equal allocation between treatment and control arms, ad using 80% power and alpha of 5%, we would need 40 subjects to complete the study. Conservatively, we expect a 10% rate of drop-out. Thus the sample size will be increased by 10% to 48 subjects (24 per arm).

Statistical analyses

Descriptive statistics (mean and 95% CI) will be reported before treatment, after treatment, and at three months follow-up for all the selected variables (clinical, instrumental and questionnaires). Specifically, TUG changes after treatments will be considered as our primary endopoint, whereas changes of all the other outcome measures (DGI, FSST, FRT, MSIS-29, MSWS-12, MFIS, BDI-II, STAI-Y, SCWT, SDMT, TAP, posturographic variables) will be treated as secondary endpoints. Between-group differences will be explored with the Wilcoxon rank-sum test. Moreover, a repeated-measures analysis of variance (within-group factor: TIME; between-group factor: TREATMENT) will be conducted to detect the main effects for treatment and time for all the available outcomes. To calculate the effect size of both treatments, we will use Cohen's d.[52] Results will be reported as mean and 95% CI. Significance will be recognized for $p < 0.05$.

Intention-to-treat

Every attempt will be made to avoid missing data through a careful check of self-reported measures, as self-administered questionnaires. An intention-to-treat analysis was carried out on all outcome measures. Missing data will be treated using the last observation carried forward approach.

Data monitoring and interim analysis

The trial does not include Data Monitoring Committee. An update on trial progress will be shared with Ferrara University Hospital Research office every six months. The research coordinator will be responsible for interim analysis to determine if the trial should stop, modify or carry out. The research group will discuss any subsequent modifications and communicate to the funding agency and Ethics Committee.

Patient and Public Involvement

The research question in this study starts from years of experience in rehabilitation of PwMS and previous research study on the use of video game therapy in balance impairment. The drafting of the study was submitted to the Multiple Sclerosis Italian Society (FISM) and reviewed to better meet patients' needs. The final version of the study reflects the collaboration between the research group and the patients' association.

Ethics and dissemination

The Ethics Committee of Ferrara approved this study with approval number 170691 on 19th 0ctober 2017. Communication of results and conclusions will be assigned to high-quality journals and national and international conferences. Results will also be disseminated through FISM annual conference. People with MS will be informed about the possible efficacy of the proposed treatment through MS support groups.

DISCUSSION

This trial may highlight the role of gaming in the rehabilitation of PwMS, enforcing the utilization of new technologies in daily clinical practice among subjects with mild to moderate disability.[53]
Our expectation from the proposed research is to observe a more significant effect on mobility, balance and dual-tasking through virtual reality training compared to a conventional approach. A meta-analysis by Casuso-Holgado et al. found that active video game training could be considered as effective as conventional training in improving balance and gait abilities in PwMS, but treatment modalities' variability among the included studies may give rise to various interpretations.[54] Furthermore, we expect different results due to the dosage of our treatment compared to those of included studies in the review and treatment administration modalities that include home-based interventions and one intervention based on telerehabilitation. Instead, our expected results are in line

with what was found by Nascimento et al. in their systematic review regarding fatigue, quality of life, and balance.[55] Making the rehabilitative session more engaging for patients may increase involvement and adherence in the rehabilitation process. Increased participation and motivation were already being observed in PwMS treated with gamified training.[53,56] Traditional rehabilitation approaches is often repetitive and boring, decreasing patient's interest and exercise participation. However, patients' satisfaction represents one of the key features for treatment adherence and rehabilitation success, particularly in PwMS.[57] Virtual reality-based therapy has been proposed to overcome the drawbacks of conventional rehabilitation, providing augmented feedback during training that contribute to a more effective motor learning.[58] Active video games may offer an enriched environment useful for subjects with neuropsychological disorders, like attentional deficit or impaired alertness. Exergaming has recently been studied as an effective strategy to improve dual-task performance in people with neurological disabilities.[59] Indeed, active video games not only engage patients in motor activities, but it simultaneously require subjects to use cognitive abilities for managing inputs into an enriched environment.[5] Therefore, we expect to observe greater modifications on cognitive and psychological evaluation of people who received rehabilitation through video game platforms. Recently, gaming consoles introduced in clinical and research settings may represent a low-cost opportunity of delivering virtual-reality training. For this reason, the use of VGT may be delivered at home, promoting self-management strategies to improve mobility function and long-term outcomes. Our study may have several limitations. First, the absence of evaluation over three months couldn't give any information about the long-term effects of active video game training. Second, we won't use any instrument to assess patients' satisfaction with the experimental treatment. Third, any neuroimaging technique will be used to show the possible neuroplastic changes in the brain due to VGT. Finally, we won't study the effects of combined treatment of VGT and other rehabilitative techniques for balance and mobility, despite combining treatments seems to augment training efficacy and boost effects of a single approach.[22] Further studies should consider these possible limitations and confirm the results related to physical and neuropsychological outcomes.

Authors' contributions

SS, GZ, AB, NB and GS conceptualized the protocol. AB, GM, GF drafted the manuscript; AB, GF, GM, NB, SS, and GS read and correct the manuscript. All authors have read and approved the final manuscript.

Funding statement

This research was supported by the Multiple Sclerosis Italian Society (Grant 2018/R/19).

Competing interests

The authors declare that they have no competing interests.

Figure 1 CONSORT flow diagram of the study

REFERENCES

1 Organization WH, Federation MSI. *Atlas : multiple sclerosis resources in the world 2008*. World Health Organization 2008

2 Khan F, Amatya B. Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. *Arch Phys Med Rehabil* 2017;**98**:353–67. doi:10.1016/j.apmr.2016.04.016

3 Cameron MH, Nilsagard Y. Balance, gait, and falls in multiple sclerosis. *Handb Clin Neurol* 2018;**159**:237–50. doi:10.1016/B978-0-444-63916-5.00015-X

4 Martin CL, Phillips BA, Kilpatrick TJ, *et al.* Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler Houndmills Basingstoke Engl* 2006;**12**:620–8. doi:10.1177/1352458506070658

5 Prosperini L, Sbardella E, Raz E, *et al.* Multiple sclerosis: white and gray matter damage associated with balance deficit detected at static posturography. *Radiology* 2013;**268**:181–9. doi:10.1148/radiol.13121695

6 Cameron MH, Lord S. Postural control in multiple sclerosis: implications for fall prevention. *Curr Neurol Neurosci Rep* 2010;**10**:407–12. doi:10.1007/s11910-010-0128-0

7 Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008;**7**:1139–51. doi:10.1016/S1474-4422(08)70259-X

8 Giazkoulidou A, Messinis L, Nasios G. Cognitive functions and social cognition in multiple sclerosis: An overview. *Hell J Nucl Med* 2019;**22 Suppl**:102–10.

9 Chalah MA, Ayache SS. Deficits in Social Cognition: An Unveiled Signature of Multiple Sclerosis. *J Int Neuropsychol Soc JINS* 2017;**23**:266–86. doi:10.1017/S1355617716001156

10 Saverino A, Waller D, Rantell K, *et al.* The Role of Cognitive Factors in Predicting Balance and Fall Risk in a Neuro-Rehabilitation Setting. *PloS One* 2016;**11**:e0153469. doi:10.1371/journal.pone.0153469

11 Negahban H, Mofateh R, Arastoo AA, *et al.* The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture* 2011;**34**:479–84. doi:10.1016/j.gaitpost.2011.06.023

12 Song J-H. The role of attention in motor control and learning. *Curr Opin Psychol* 2019;**29**:261–5. doi:10.1016/j.copsyc.2019.08.002

13 Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2015;**21**:123–31. doi:10.1177/1352458514547408

14 Chamard Witkowski L, Mallet M, Bélanger M, *et al.* Cognitive-Postural Interference in Multiple Sclerosis. *Front Neurol* 2019;**10**:913. doi:10.3389/fneur.2019.00913

15 Ruggieri S, Fanelli F, Castelli L, *et al.* Lesion symptom map of cognitive-postural interference in multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2018;**24**:653–62. doi:10.1177/1352458517701313

16 Sosnoff JJ, Wajda DA, Sandroff BM, *et al.* Dual task training in persons with Multiple Sclerosis: a feasability randomized controlled trial. *Clin Rehabil* 2017;**31**:1322–31. doi:10.1177/0269215517698028

17 Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Interv Aging* 2017;**12**:557–77. doi:10.2147/CIA.S125201

18 Rooney S, Ozkul C, Paul L. Correlates of dual-task performance in people with multiple sclerosis: A systematic review. *Gait Posture* 2020;**81**:172–82. doi:10.1016/j.gaitpost.2020.07.069

19 Mulder T, Zijlstra W, Geurts A. Assessment of motor recovery and decline. *Gait Posture* 2002;**16**:198–210. doi:10.1016/s0966-6362(01)00157-6

20 Laver KE, Lange B, George S, *et al.* Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev* 2017;**11**:CD008349. doi:10.1002/14651858.CD008349.pub4

21 Forsberg A, Nilsagård Y, Boström K. Perceptions of using videogames in rehabilitation: a dual perspective of people with multiple sclerosis and physiotherapists. *Disabil Rehabil* 2015;**37**:338–44. doi:10.3109/09638288.2014.918196

22 Maggio MG, Russo M, Cuzzola MF, *et al.* Virtual reality in multiple sclerosis rehabilitation: A review on cognitive and motor outcomes. *J Clin Neurosci Off J Neurosurg Soc Australas* 2019;**65**:106–11. doi:10.1016/j.jocn.2019.03.017

23 Schaeffer E, Busch J-H, Roeben B, *et al.* Effects of Exergaming on Attentional Deficits and Dual-Tasking in Parkinson's Disease. *Front Neurol* 2019;**10**:646. doi:10.3389/fneur.2019.00646

24 Parra-Moreno M, Rodríguez-Juan JJ, Ruiz-Cárdenas JD. Use of commercial video games to improve postural balance in patients with multiple sclerosis: A systematic review and meta-analysis of randomised controlled clinical trials. *Neurol Barc Spain* Published Online First: 7 March 2018. doi:10.1016/j.nrl.2017.12.001

25 Brichetto G, Spallarossa P, de Carvalho MLL, *et al.* The effect of Nintendo® Wii® on balance in people with multiple sclerosis: a pilot randomized control study. *Mult Scler Houndmills Basingstoke Engl* 2013;**19**:1219–21. doi:10.1177/1352458512472747

26 Pitteri M, Dapor C, Ziccardi S, *et al.* Visual-Attentional Load Unveils Slowed Processing Speed in Multiple Sclerosis Patients: A Pilot Study with a Tablet-Based Videogame. *Brain Sci* 2020;**10**. doi:10.3390/brainsci10110871

27 Bove R, Rowles W, Zhao C, *et al.* A novel in-home digital treatment to improve processing speed in people with multiple sclerosis: A pilot study. *Mult Scler Houndmills Basingstoke Engl* 2021;**27**:778–89. doi:10.1177/1352458520930371

28 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586. doi:10.1136/bmj.e7586

29 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**:1444–52. doi:10.1212/wnl.33.11.1444

30 Kalron A, Dolev M, Givon U. Further construct validity of the Timed Up-and-Go Test as a measure of ambulation in multiple sclerosis patients. *Eur J Phys Rehabil Med* 2017;**53**:841–7. doi:10.23736/S1973-9087.17.04599-3

31 Beatty WW, Goodkin DE. Screening for cognitive impairment in multiple sclerosis. An evaluation of the Mini-Mental State Examination. *Arch Neurol* 1990;**47**:297–301. doi:10.1001/archneur.1990.00530030069018

32 Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332. doi:10.1136/bmj.c332

33 Straudi S, Severini G, Sabbagh Charabati A, *et al.* The effects of video game therapy on balance and attention in chronic ambulatory traumatic brain injury: an exploratory study. *BMC Neurol* 2017;**17**:86. doi:10.1186/s12883-017-0871-9

34 Nilsagård YE, Forsberg AS, von Koch L. Balance exercise for persons with multiple sclerosis using Wii games: a randomised, controlled multi-centre study. *Mult Scler Houndmills Basingstoke Engl* 2013;**19**:209–16. doi:10.1177/1352458512450088

35 Bonnechère B, Jansen B, Omelina L, *et al.* The use of commercial video games in rehabilitation: a systematic review. *Int J Rehabil Res Int Z Rehabil Rev Int Rech Readaptation* 2016;**39**:277–90. doi:10.1097/MRR.0000000000000190

36 Cano Porras D, Siemonsma P, Inzelberg R, *et al.* Advantages of virtual reality in the rehabilitation of balance and gait: Systematic review. *Neurology* 2018;**90**:1017–25. doi:10.1212/WNL.0000000000005603

37 Eftekharsadat B, Babaei-Ghazani A, Mohammadzadeh M, *et al.* Effect of virtual reality-based balance training in multiple sclerosis. *Neurol Res* 2015;**37**:539–44. doi:10.1179/1743132815Y.0000000013

38 Mañago MM, Cameron M, Schenkman M. Association of the Dynamic Gait Index to fall history and muscle function in people with multiple sclerosis. *Disabil Rehabil* 2020;**42**:3707–12. doi:10.1080/09638288.2019.1607912

39 Moore M, Barker K. The validity and reliability of the four square step test in different adult populations: a systematic review. *Syst Rev* 2017;**6**:187. doi:10.1186/s13643-017-0577-5

40 Soke F, Eldemir S, Ozkan T, *et al.* The functional reach test in people with multiple sclerosis: a reliability and validity study. *Physiother Theory Pract* 2021;:1–15. doi:10.1080/09593985.2021.1938308

41 Hobart J, Lamping D, Fitzpatrick R, *et al.* The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain J Neurol* 2001;**124**:962–73.

42 Marengo D, Rosato R, Gamberini G, *et al.* Examining the validity of the multiple-sclerosis walking scale-12 with Rasch analysis: Results from an Italian study. *Mult Scler Relat Disord* 2019;**36**:101400. doi:10.1016/j.msard.2019.101400

43 Rooney S, McFadyen DA, Wood DL, *et al.* Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis. *Mult Scler Relat Disord* 2019;**35**:158–63. doi:10.1016/j.msard.2019.07.028

44 Coghe G, Corona F, Marongiu E, *et al.* Fatigue, as measured using the Modified Fatigue Impact Scale, is a predictor of processing speed improvement induced by exercise in patients with multiple sclerosis: data from a randomized controlled trial. *J Neurol* 2018;**265**:1328–33. doi:10.1007/s00415-018-8836-5

45 Sacco R, Santangelo G, Stamenova S, *et al.* Psychometric properties and validity of Beck Depression Inventory II in multiple sclerosis. *Eur J Neurol* 2016;**23**:744–50. doi:10.1111/ene.12932

46 Santangelo G, Sacco R, Siciliano M, *et al.* Anxiety in Multiple Sclerosis: psychometric properties of the State-Trait Anxiety Inventory. *Acta Neurol Scand* 2016;**134**:458–66. doi:10.1111/ane.12564

47 Zimmermann P, Fimm B. A test battery for attentional performance. In: *Applied Neuropsychology of Attention. Theory, Diagnosis and Rehabilitation*. 2002. 110–51.

48 Coghe G, Pilloni G, Zucca E, *et al.* Exploring cognitive motor interference in multiple sclerosis by the visual Stroop test. *Mult Scler Relat Disord* 2018;**22**:8–11. doi:10.1016/j.msard.2018.02.026

49 Benedict RH, DeLuca J, Phillips G, *et al.* Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2017;**23**:721–33. doi:10.1177/1352458517690821

50 Sun R, Moon Y, McGinnis RS, *et al.* Assessment of Postural Sway in Individuals with Multiple Sclerosis Using a Novel Wearable Inertial Sensor. *Digit Biomark* 2018;**2**:1–10. doi:10.1159/000485958

51 Severini G, Straudi S, Pavarelli C, *et al.* Use of Nintendo Wii Balance Board for posturographic analysis of Multiple Sclerosis patients with minimal balance impairment. *J Neuroengineering Rehabil* 2017;**14**:19. doi:10.1186/s12984-017-0230-5

52 Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. New York: : Routledge 1988. doi:10.4324/9780203771587

53 Dalmazane M, Gallou-Guyot M, Compagnat M, *et al.* Effects on gait and balance of home-based active video game interventions in persons with multiple sclerosis: A systematic review. *Mult Scler Relat Disord* 2021;**51**:102928. doi:10.1016/j.msard.2021.102928

54 Casuso-Holgado MJ, Martín-Valero R, Carazo AF, *et al.* Effectiveness of virtual reality training for balance and gait rehabilitation in people with multiple sclerosis: a systematic review and meta-analysis. *Clin Rehabil* 2018;**32**:1220–34. doi:10.1177/0269215518768084

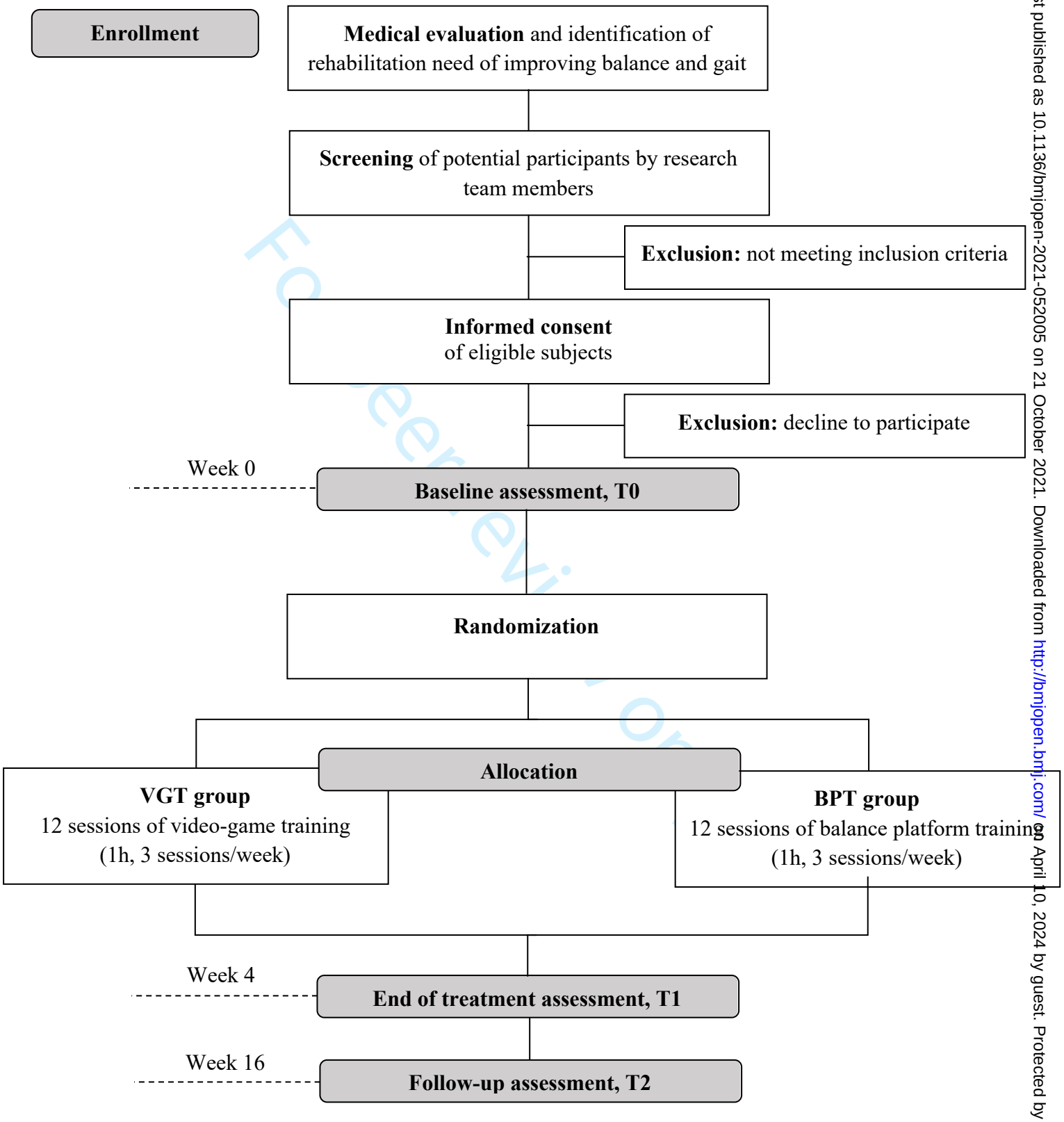
55 Nascimento AS, Fagundes CV, Mendes FADS, *et al.* Effectiveness of Virtual Reality Rehabilitation in Persons with Multiple Sclerosis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Mult Scler Relat Disord* 2021;**54**:103128. doi:10.1016/j.msard.2021.103128

56 Sokolov AA, Grivaz P, Bove R. Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. *Curr Treat Options Neurol* 2018;**20**:53. doi:10.1007/s11940-018-0538-x

57 Jeong IC, Liu J, Finkelstein J. Factors Affecting Adherence with Telerehabilitation in Patients with Multiple Sclerosis. *Stud Health Technol Inform* 2019;**257**:189–93. doi:10.3233/978-1-61499-951-5-189

58 Meca-Lallana V, Prefasi D, Alabarcez W, *et al.* A Pilot Study to Explore Patient Satisfaction With a Virtual Rehabilitation Program in Multiple Sclerosis: The RehabVR Study Protocol. *Front Neurol* 2020;**11**:900. doi:10.3389/fneur.2020.00900

59 Mura G, Carta MG, Sancassiani F, *et al.* Active exergames to improve cognitive functioning in neurological disabilities: a systematic review and meta-analysis. *Eur J Phys Rehabil Med* 2018;**54**:450–62. doi:10.23736/S1973-9087.17.04680-9



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Università degli Studi di Ferrara

ARCISPEDALE S. ANNA
DIPARTIMENTO DI NEUROSCIENZE/RIABILITAZIONE

Foglio informativo per il paziente

Gentile Signora/e,
Lei è invitata/o a partecipare ad uno studio che viene effettuato presso questo ospedale cui lei si è rivolto per motivi di diagnosi o cura. Si prenda tutto il tempo necessario per leggere questo foglio. Se qualcosa non le è chiaro, non esiti a porre tutte le domande che vorrà.

Il titolo dello studio è:

Il ruolo della video game terapia sull'equilibrio e le funzioni cognitive in pazienti con sclerosi multipla e disabilità lieve o moderata. Uno studio pilota randomizzato controllato.

Perché questo studio clinico viene proposto?
Spesso la Sclerosi Multipla si caratterizza per la presenza sia di disordini dell'equilibrio, sia di disordini cognitivi, cioè quelle funzioni del cervello quali l'attenzione e la memoria. Gli aspetti cognitivi non devono essere considerati come una dimensione separata dagli aspetti motori, ad esempio l'attenzione agisce sul controllo dell'equilibrio. Inoltre, nella vita quotidiana è possibile osservare la compresenza dei due aspetti: basti pensare a quando si cammina e contemporaneamente si parla. Il trattamento riabilitativo dovrebbe quindi tenere conto di entrambi questi aspetti, proponendo attività che potenzino la performance sia cognitiva che motoria. La Video-Game Terapia potrebbe essere uno strumento utile in tal senso, in quanto può favorire il trattamento sia dell'equilibrio sia degli aspetti cognitivi contemporaneamente. Inoltre, rispetto a trattamenti più "classici", la Video-game Terapia aumenta la motivazione, favorendo l'acquisizione di nuove competenze. E' inoltre meno dispendiosa e più "versatile" in quanto è possibile proseguire il trattamento riabilitativo anche al domicilio. Con questo studio esplorativo vogliamo confrontarne gli effetti rispetto ai trattamenti "classici" per l'equilibrio, sia per quanto riguarda il miglioramento dell'equilibrio, sia delle funzioni cognitive in generale.

Lo scopo principale di questo studio è quello di verificare gli effetti di un terapia mediante un dispositivo commercialmente disponibile sull'equilibrio e sulle funzioni cognitive nei pazienti SM deambulanti rispetto a un trattamento riabilitativo "standard". In secondo luogo, esploreremo gli effetti in altri settori che sono generalmente compromessi nella popolazione MS e che possono essere migliorati mediante riabilitazione motoria, come il benessere psicologico, la stanchezza e la qualità di vita.

Quali sono le caratteristiche di questo studio?
Lo studio prevede di raccogliere dati di sicurezza ed efficacia di una procedura confrontata con quella attualmente in uso secondo le norme di buona pratica clinica.
Verrà reclutato un campione di pazienti con Sclerosi Multipla presso l'Azienda Ospedaliero - Universitaria di Ferrara. I soggetti reclutati saranno attribuiti in maniera casuale in gruppi che riceveranno la Video Game Terapia (VGT) o la Terapia mediante Piattaforma dell'Equilibrio (BPT).
Il gruppo sperimentale riceverà 12 sessioni di allenamento VGT (3 volte alla settimana) per 4 settimane. Il gruppo di controllo riceverà la stessa quantità di sessioni BPT. Selezioneremo le misure di equilibrio che esplorano un'ampia gamma di compiti motori. Saranno inoltre somministrati test per valutare l'affaticamento, le funzioni cognitive e il benessere fisico e psicologico. L'equilibrio verrà valutato mediante una serie di test

clinici funzionali che indagano un'ampio spettro di compiti motori. Inoltre verrà eseguito un esame della postura attraverso una pedana in grado di misurare le oscillazioni corporee in posizione eretta. Verranno somministrati questionari per valutare la fatica, il benessere psicofisico e la qualità di vita. Le misure verranno raccolte prima del trattamento (T0), alla fine (T1) e a distanza di 3 mesi (T2) per valutare il mantenimento dei risultati.

Chi propone lo studio?
Lo Studio è proposto dal Settore di Medicina Riabilitativa "S. Giorgio" – Dipartimento di Neuroscienze/Riabilitazione dell'Azienda Ospedaliero-Universitaria di Ferrara.

Perché sono invitato a partecipare allo studio?
Le stiamo proponendo di partecipare a questo studio perché è affetto da Sclerosi Multipla
E' previsto che partecipino a questo studio 48 pazienti.

Cosa comporta la partecipazione allo studio, rispetto al normale percorso diagnostico-terapeutico per la mia malattia?
Lo studio prevede la creazione di due gruppi di pazienti: il primo gruppo riceverà la Video-Game Terapia, mentre il secondo gruppo riceverà un trattamento mediante Piattaforma dell'Equilibrio. L'attribuzione ad un gruppo o ad un altro è casuale. Prima dell'inizio del trattamento, alla fine del trattamento e a distanza di tre mesi, verranno effettuate misurazioni attraverso specifici test, così da permettere un confronto tra i due gruppi.

Quali rischi o inconvenienti potrei avere dalla partecipazione a questo studio?
Non vi sono rischi legati allo studio.
Eventuali nuove informazioni che potrebbero influenzare la sua volontà di partecipazione le verranno comunicate il più presto possibile. Lo stesso vale per una eventuale interruzione o sospensione dello studio.

Quali vantaggi potrei avere nel partecipare a questo studio?
Lei potrebbe non avere beneficio diretto dalla partecipazione. Questo studio potrà contribuire a migliorare la diagnosi e la comprensione della sua malattia, e portare allo sviluppo di nuovi trattamenti riabilitativi per i disturbi dell'equilibrio e cognitivi. I risultati dello studio saranno poi pubblicati su riviste scientifiche nazionali o internazionali. Per la partecipazione allo studio non è previsto alcun compenso.

Sono obbligato a partecipare allo studio?
No. La decisione di partecipare è assolutamente libera. Se lei acconsente ha la possibilità di contribuire alla ricerca medica attraverso questo studio. Se però non vuole partecipare, non deve fornire alcuna spiegazione. Il suo rifiuto non influenzerà in alcun modo il trattamento che le verrà proposto, e riceverà comunque tutte le terapie previste dalla buona pratica clinica per la sua patologia.

Potrò cambiare idea dopo aver accettato di partecipare?
Sì. La decisione di partecipare allo studio è volontaria e libera, e lei ha il diritto di revocare il suo consenso in qualunque momento lo desideri, senza fornire spiegazioni e senza che questo influenzi in alcun modo il trattamento che le verrà proposto, che sarà comunque il migliore disponibile.

Se partecipo allo studio, miei dati personali e clinici saranno noti a tutti?
No. I suoi dati clinici saranno resi anonimi. Il suo nome e cognome saranno sostituiti da un codice che solo il responsabile dello studio conoscerà.

Trattamento dei dati
Se Lei deciderà di partecipare allo studio, tutti i dati raccolti (età, sesso, origine etnica e i dati clinici), saranno archiviati elettronicamente in maniera rigorosamente anonima, ai sensi del Decreto Legislativo n. 196/03 sulla tutela delle persone rispetto al trattamento dei dati personali e saranno trattati in modo assolutamente riservato. I dati verranno conservati presso l'unità Operativa di Medicina Riabilitativa S.

Giorgio dell'Azienda Ospedaliero-Universitaria di Ferrara per un periodo di 2 anni dalla chiusura dello studio. La persona responsabile della gestione dei suoi dati per questo studio e reparto è la dr.ssa Sofia Straudi.
L'accesso diretto alla sua documentazione sarà consentito a tutti coloro che sono coinvolti nell'effettuazione dello studio (personale sanitario, personale che elabora i dati, personale ispettivo e quant'altri abilitati dal protocollo di studio e/o dalle normative vigenti) e alle autorità regolatorie nella misura permessa dalle leggi senza violare la sua riservatezza.

Il medico della ricerca le consegnerà una lettera rivolta al suo medico di base, per informarlo della sua partecipazione allo studio, per la migliore conduzione clinica dello stesso.

Chi ha approvato lo studio?
Il protocollo dello studio è stato redatto in accordo con la dichiarazione di Helsinki sull'etica della ricerca in medicina ed è stato approvato dal Comitato Etico di questo ospedale.
Se Lei accetterà di partecipare a questo studio Le verrà chiesto di **firmare e datare** di suo pugno questo foglio informativo di cui Le sarà consegnata copia assieme alla copia del foglio di consenso.

A chi posso rivolgermi se ho dei problemi durante lo studio?
Il medico referente per questo studio è la Dr.ssa Sofia Straudi Tel. 0532-236185 (s.straudi@ospfe.it)
Lo staff operativo coinvolto nello studio è costituito dai seguenti operatori:
1) Andrea Baroni (a.baroni@ospfe.it)
2) Nino Basaglia
3) Anna Scotti
4) Giada Milani
5) Giulia Fregna

Nome in stampatello del partecipante allo studio

_____

Data e Firma

_____

Nome in stampatello del Medico ricercatore

_____

Data e Firma

Il ruolo della video game terapia sull'equilibrio e le funzioni cognitive in pazienti con sclerosi multipla e disabilità lieve o moderata. Uno studio pilota randomizzato controllato.

Modulo di consenso allo studio e al trattamento dei dati

Questo modulo deve essere firmato da Lei solo nel caso decida di partecipare allo studio. E' importante che Lei abbia discusso approfonditamente con il Medico prima di firmare questo consenso, anche sulla base del foglio informativo a cui esso si riferisce. Partecipano allo studio solo i Pazienti che accettano. Il Paziente può ritirare il suo consenso in ogni momento.

Dichiaro di ricevere copia firmata del presente modulo di consenso unitamente a copia datata e firmata del foglio informativo. Dichiaro inoltre di:

- aver ricevuto dal medico esaurienti spiegazioni in merito alla richiesta di partecipazione allo studio, in particolare sulle finalità e sulle procedure;
- aver letto e compreso il foglio informativo che mi è stato consegnato con sufficiente anticipo e che conferma quanto mi è stato spiegato a voce;
- aver avuto la possibilità di porre domande ed aver avuto risposte soddisfacenti;
- farmi carico della consegna della lettera relativa allo studio per il mio medico di famiglia;
- essere consapevole che la partecipazione è volontaria, con l'assicurazione che il rifiuto a partecipare non influirà sulla scelta della terapia migliore per me;
- essere consapevole che, se ritirerò il mio consenso, i dati raccolti prima del ritiro del consenso saranno utilizzati dal ricercatore;
- autorizzare il trattamento dei miei dati personali ai sensi del Decreto legislativo n. 196/2003 (codice privacy) con le finalità indicate nello studio
- Acconsento a partecipare allo studio clinico suddetto

Nome in stampatello del partecipante allo studio

Luogo e Data nascita_____

Residenza:

Data e Firma

_____

Nome in stampatello del Medico ricercatore

_____

Data e Firma

_____

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**1, 3**
	2b	All items from the World Health Organization Trial Registration Data Set	**-**
Protocol version	3	Date and version identifier	**8**
Funding	4	Sources and types of financial, material, and other support	**8**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 2, 8**
	5b	Name and contact information for the trial sponsor	**1**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**8**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**7, 8**

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

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**7**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**2**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**3**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**3**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**3**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**3**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**3**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**5**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**4**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**7**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**7**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**7**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**7**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**7**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**7**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**4, 7**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**7**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**3**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**-**

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**2, 3**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**not applicable**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**3**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**8**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**-**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**not applicable**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**8**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**not present**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**not present**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**sent to editorial office_**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**not applicable**

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