Home-based EXergames To impRove cognitivE function in MUltiple Sclerosis:

the EXTREMUS study

A multicenter, randomized, single-blind non-inferiority trial

Version 1.0, 02 Novembre 2018

Supported by FISM (Fondazione Italiana Sclerosi Multipla) cod. 2017/R/22 and financed or co-financed with the '5 per mille' public funding

EudraCT number: NOT APPLICABLE

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ABBREVIATIONS

2MWT	2-Minute Walk Test
AE	Adverse Event
AISM	Associazione Italiana Sclerosi Multipla
ANCOVA	Analysis of Covariance
BDI-II	Beck Depression Inventory (2nd version)
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BVMT-R	Brief Visuospatial Memory Test–Revised
CMI	Cognitive-Motor Interference
COGNI-TRAcK	Cognitive Training Kit
CRF	Case Report Form
CRIQ	Cognitive Reserve Index Questionnaire
CVLT2	California Verbal Learning Test
DMT	Disease-Modifying Treatment
EDSS	Expanded Disability Status Scale
FISM	Fondazione Italiana Sclerosi Multipla
GCP	Good Clinical Practice
HLAQ	Historical Leisure Activity Questionnaire
IEC	Institutional Ethical Committee
MFIS-21	21-item Modified Fatigue Impact Scale
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29	29-item Multiple Sclerosis Impact Scale
PASAT	Paced Auditory Serial Addition Test
PI	Principal Investigator
PROs	Patient-Reported Outcomes
RM-ANOVA	Repeated Measures Analysis of the Variance
SCWT	Stroop Color-Word Test
SDMT	Symbol Digit Modalities Test
TCI	Temperament and Character Inventory
WHO	World Health Organization
WPAI:MS	Work Productivity and Activity Impairment: Multiple Sclerosis

PROTOCOL SYNOPSIS

Study design
Phase II, multicenter, randomized, sham-controlled, single-blind, parallel arm, multicenter study to test the hypothesis that home-based exergames is not inferior to home-based cognitive rehabilitation delivered by a software application (app) for mobile devices and both interventions are superior to a placebo-analogue cognitive intervention in improving cognitive function and reducing cognitive-motor interference in people with MS.

Study duration
Overall 16 weeks from randomization (8 weeks of intervention plus 8 weeks of follow-up following the intervention).

Target population
Patients with MS according to 2010 revised McDonald criteria, regardless of disease course (relapsing-remitting, secondary progressive, primary progressive), presenting a clinically relevant deficit in sustained attention and information processing speed.

Investigational interventions

Exergames: home-based repetition of several games delivered by the Nintendo © Wii Balance Board, a commercial off-the-shelf video game console for re-training of balance and postural strategies

Adaptive COGNI-TRAcK**:** adaptive (i.e. automatic adjustment of tasks difficulty) working memory training delivered by a customized application software for mobile devices to self-administer at-home

Sham COGNI-TRAcK: non-adaptive (i.e. constant difficulty level) working memory training delivered by the same app as afore described

Study procedures
Participants will be randomized in a 1:1:1 ratio to receive an 8-week home-based training with exergames (intervention of interest) or adaptive COGNI-TRAcK (comparator intervention) or sham COGNI-TRAcK (placebo-analogue intervention). Study assessment will be done at study enrolment (baseline), at the end of the 8-week intervention period (immediate post-training, Week 8) and after 16 weeks from randomization (post-training follow-up, Week 16).

Sample size estimation
We estimated a pre-defined 8-point non-inferiority margin, based on a significant effect of the COGNI-TRAcK in inducing an about 8-point mean increase at SDMT score (with respect to a sham intervention). Accordingly, 35 subjects per arm are required to ensure, with an approximately 85%-power level, that the lower limit of a one-side 95% confidence interval will be above the pre-defined non-inferiority margin. Therefore, considering also a drop-out rate of 25%, a total of 132 subjects should be enrolled.

Statistical methods
All analysis will be based on the intention-to-treat principle using the fully analysis dataset including all randomized patients. Missing data will be handled by multiple imputation method. Continuous data will be analyzed by parametric and non-parametric RM-ANOVAs with effect size estimation. The time-to-event data will be analyzed by Kaplan-Meier curves and Log-Rank test with a factor for treatment group.
An interim analysis will be conducted when at least 50% of the estimated sample size will complete the 8-week intervention period.

Study objectives

Primary objective	**Primary endpoint**
To demonstrate not inferior efficacy of exergames over COGNI-TRAcK and superior efficacy of both interventions over sham in improving sustained attention and information processing speed	Change at the SDMT from baseline to Week 8
Secondary objectives	**Secondary endpoints**
To demonstrate not inferior efficacy of exergames over COGNI-TRAcK and superior efficacy of both interventions over sham in improving cognitive functions	Change at the BICAMS and SCWT from baseline to Week 8
Additional objectives	**Additional endpoints**
To demonstrate not inferior efficacy of exergames over COGNI-TRAcK and superior efficacy of both interventions over sham in reducing the impact of MS on: - cognitive-motor interference - activities of daily living - fatigue - work productivity	Change of dual-task cost of walking and balance as estimated by the 2MWT and static posturography in dual-task *vs.* single-task condition from baseline to Week 8 Change at the MSIS-29 from baseline to Week 8 Change at the MFIS from baseline to Week 8 Change at the WPAI:MS from baseline to Week 8
Exploratory objectives	**Exploratory endpoints**
To demonstrate not inferior efficacy of exergames over COGNI-TRAcK and superior efficacy of both interventions over sham on: - physical activity - adherence	Physical activity measured by wearable actigraph Percentage of training completed at home
Safety objectives	**Safety endpoints**
To demonstrate the safety of exergames and COGNI-TRAcK over sham on the risk of: - accidental falls - adverse events	Time from randomization to the first accidental fall Proportion of patients with at least an adverse event from baseline to Week 8 and to Week 16

INTRODUCTION

Background and rationale for conducting the study

Cognitive impairment is common in people with multiple sclerosis (MS), frequently involving domains such as information processing speed, episodic memory, sustained attention, concentration and aspects of executive functions [1],[2]. Cognitive dysfunction can affect patients at any stage of the disease, from radiologically isolated syndrome to later phases of MS [3],[4].

There is no effective pharmacological treatment to manage cognitive impairment in MS [5]. Therefore, rehabilitation remains the only strategy to limit the impact of this dysfunction on quality of life. Encouraging results have been reported with computer-assisted training specifically focused on information processing, attention, and executive functions and performed with dedicated software [6]. Unfortunately, the time and costs of these cognitive rehabilitative programmes limit their applicability in the real life.

To increase the complexity of MS management, very often people with MS have coexisting cognitive and motor deficits and require both cognitive and motor rehabilitation. **Therefore, providing a single rehabilitative strategy that can address cognitive and motor issues remains highly desirable.**

Exergaming (i.e. playing exergames) is a form of whole-body physical exercise performed through active video games. It involves not only the hand-eye coordination, but also whole body physical exertion, with the aim of improving fitness and promoting an active lifestyle [7]. The potential of exergames in rehabilitation has been established after the 2000s, through the increased availability of off-the-shelf commercial platforms, such as the Nintendo Wii, Microsoft Xbox Kinect and Sony PlayStation Move. The use of these commercial devices for neurorehabilitation has been recently included into the definition of virtual reality (VR)-based training and is considered an example of non-immersive VR environment [8]. Research with exergames has focused mainly on promotion of physical activity in the general population and in a variety of neurological cohorts, including MS [7]. In people with MS, exergames have been reported to be safe in home setting [9], as well as effective in improving balance, walking speed, muscle strength, dual-task performance, quality of life, fitness level and adherence to exercise [10]–[14]. Using advanced magnetic resonance imaging (MRI), enhanced brain structural plasticity has been described after a 12-weeks of home-based intervention with the Wii balance board [15]. As an intervention, exergaming encompasses most of the principles underlying experience-dependent neural plasticity [16], such as high-intensity repetition of task-oriented exercises, incrementally increase of task difficulty, real-time feedback, salience, motivation and reward, and even transfer effect [17]. Therefore, it has the potential of offering an integrated and adaptable training to improve functions across a variety of domains, from motor to cognitive with interference solving, planning, reasoning, working memory and multi-tasking skills [18]. Evidence in the general population and in older adults suggests that action video games can transfer their beneficial effects from motor to cognitive skills [19],[20]. Meta-analyses of studies on action video gaming effects in healthy subjects and clinically impaired populations reveal small to medium effect sizes on a series of cognitive skills [21],[22]. However, when considering only patients with neurological disabilities, exergames are equally effective for global cognitive functions and attention, and more effective for executive functions and visuo-spatial perception, compared with conventional therapies. Despite the afore mentioned meta-analyses, there are only few studies investigating the effect of exergames on cognitive function in MS [12],[23] and none that was designed to specifically test the hypothesis of using exergaming to improve cognitive function in MS.

Rationale for study design and duration

This is a multi-centre, 16-week (8-week intervention followed by 8-week follow-up), randomized, single-blind, parallel-arm study comparing three different types of home-based training:

(1) active video games of balance delivered by the Wii balance board, from here onwards called **'exergames'** (intervention of interest);

(2) Cognitive Training Kit (COGNI-TRAcK) with increasing difficulty levels, from here onwards called **'adaptive COGNI-TRAcK'** (comparator intervention);

(3) COGNI-TRAcK at constant difficulty level, from here onwards called **'sham COGNI-TRAcK'** (placebo-analogue intervention) [24].

This study design will allow us to test the hypotheses that (i) exergames and adaptive COGNI-TRAcK are more effective than sham adaptive COGNI-TRAcK; (ii) exergames are not inferior to adaptive COGNI-TRAcK.
The choice of an 8-week study duration was based on previously published papers on cognitive training delivered by COGNI-TRAcK. In this study, 8 weeks of adaptive COGNI-TRAcK training were sufficient to determine a significant improvement in the SDMT score when compared with sham COGNI-TRAcK, yielding to a post-training between-arm difference of 8 points ($p<0.001$) [24].
The 8-week post-training follow-up period will allow us to investigate the retention of training effect, which is an underinvestigated topic in MS rehabilitation setting. Literature data provide conflicting results (no retention for exergames, 6-month retention for cognitive rehabilitation) [9],[24].

Rationale for interventions
Exergames (the portmanteaux for “exercise” and “video games”) represent a form of whole-body physical exercise performed through active video games. Playing exergames involves not only the hand-eye coordination, but also whole body physical exertion, with the aim of improving fitness and promoting an active lifestyle [8]. Unlike the fully immersive VR (that simulates a lifelike multisensorial experience in a 3-dimensional artificial environment), the non-immersive VR involves the use of smaller-scale, 2- dimensional environment (e.g. home TV, computer display, etc) and interface devices, such as balance board, motion controllers or cameras equipped with depth sensors that can also provide haptic or kinesthetic communication reproducing tactile sensations by applying forces, vibrations or motions [7].
A recent meta-analysis exploring the role of exergames in improving cognitive functions in persons suffering from neurological disabilities (including MS), showed that exergames significantly improved executive functions and visuo-spatial perception when compared to alternative or no intervention [22]. Therefore, exergames can represent a highly-flexible tool to rehabilitate both cognitive and motor functions by means of an unique training.

COGNI-TRAcK is a low-cost, user-friendly application software (app) for portable devices (mobile phone and tablet) that delivers a self-administered, intensive and monitored cognitive training based on working memory exercises. The main feature of COGNI-TRAcK is the implementation of automatic adaptive working load algorithms and procedures for intensiveness regulation. Moreover, it can be easily used at home enhancing the possibility to schedule an intensive training and ensuring adherence to treatment. Preliminary data showed that COGNI-TRAcK is highly usable, motivating and well-accepted by patients with MS [25].
Adaptive COGNI-TRAcK (i.e. automatic adjustment of tasks difficulty) has been found superior over sham COGNI-TRAcK (i.e. constant difficulty level) in verbal memory acquisition and delayed recall, verbal fluency, sustained attention, concentration and information processing speed [24]. Therefore, sham COGNI-TRAcK can be used as placebo-analogue arm in order to avoid ethical concerns and a possible unmotivating effect of wait-list group.

Rationale for study endpoints
The SDMT (primary endpoint) represents a simple screening test for cognitive impairment [26],[27]. An improvement of 4 points or 10% in magnitude is considered clinically relevant [28].
The Brief International Cognitive Assessment for MS (BICAMS) (secondary endpoint) has been recently developed as brief, practical and universal assessment tool for cognitive impairment in MS; it includes the SDMT, the California Verbal Learning Test-2 (CVLT2) and the Brief Visuospatial Memory Test–Revised (BVMT-R) [29]. To test some aspects of executive functions not explored by the BICAMS, the Stroop Color-Word Test (SCWT) is also included in the assessment [30].
Measurements of Cognitive-Motor Interference (CMI) and Patient-Reported Outcomes (PROs) for assessing activities of daily living, fatigue and work productivity (additional endpoints), as well as measurements of physical activity by actigraph and adherence to protocol (additional endpoints) provide data to evaluate the extent to which an improvement in primary and secondary endpoints can be transferred into real world activity (i.e. ecological validity) and acceptability for patients.
Occurrence and timing of adverse events (AEs), with particular attention for accidental falls, provide data on safety of home-based, minimally assisted interventions.

Risk:benefit ratio and ethical consideration

Cognitive dysfunction and motor impairment are disabling symptom in people with MS across all disease stages. The present study will test the efficacy and safety of a novel rehabilitation approach that can be used in a home care setting for exploiting and promoting – by using a single training session – the combined motor and cognitive function of specific brain regions using exergames.

Results from published studies indicated a positive risk:benefit ratio for exergames, with no or only minor AEs [9]. Pilot studies with home-based exergames have reported indeed no increased risk of accidental falls and only minor musculo-skeletal problems solved with training discontinuation or at least standard treatment [9]. No AE or side effects are reported for home-based COGNI-TRAcK. Therefore, low-cost, commercial, minimally supervised exergames can potentially offer a cost-efficacy profile at least equal (or even better, as previously reported) than standard rehabilitation care, through the reduction in transport and staffing costs [11].

METHODS

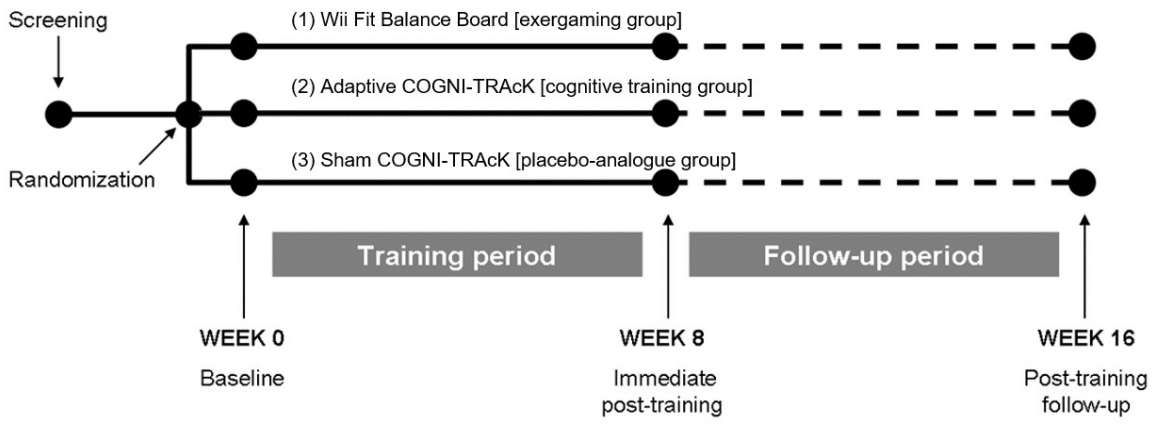
Study design

This is a phase II, multicenter, randomized, sham-controlled, single-blind, parallel group, multicenter study to test the hypothesis that home-based exergames is not inferior to home-based cognitive rehabilitation delivered by a software application (app) for mobile devices and both interventions are superior to a placebo-analogue intervention in improving cognitive function and reducing cognitive-motor interference in people with MS.

Participants

Patients with MS, regardless of disease course, who fulfil all inclusion criteria and none of the exclusion criteria, will be randomized in a 1:1:1 ratio to exergames or adaptive COGNI-TRAcK or sham COGNI-TRAcK. This study includes two periods (training period and follow-up period) and three visits (see the **FIGURE** below):

- on Week 0, at study enrolment/randomization (baseline visit);
- on Week 8 (+/- 5 days), i.e. after the end of the 8-week training period (Week 8 visit);
- on Week 16 (+/-5 days), i.e. at study termination after the 8-week post-training follow-up period (Week 16 visit).



Eligibility criteria

For inclusion:
(i) age between 18 and 55 years (inclusive);
(ii) cognitive impairment, defined as failure in the SDMT, defined as a corrected score less than 38, i.e. below the 5th percentile of normative value [31];
(iii) Expanded Disability Status Scale (EDSS) score between 2.0 and 5.5 [32];
(iv) ability to stand upright for at least 180 seconds without any support;
(v) ability to understand and comply with study requirements;
(vi) ability to provide a valid informed consent before any study procedure.

For exclusion:
(i) relapse in the previous 6 months;
(ii) initiation of disease-modifying or symptomatic treatments or physiotherapy programme in the 3 months prior to study entry;
(iii) any medication/physiotherapy changes occurring over the previous 3 months;
(iv) significant visual impairment, defined as a Visual System scoring more than 2 at the Kurtzke Functional Systems Score [32];
(v) clinically relevant depression, defined as Beck Depression Inventory-II (BDI-II) score equal or more than 14 [33];
(vi) overt dementia, defined as an adjusted Mini Mental State Examination (MMSE) score equal or less than 24 [34];
(vii) history of epilepsy or seizures;
(viii) any medical condition, including musculoskeletal disorders that can interfere with the study conduction.

Randomization procedure
Randomization codes will be computer-generated in blocks of six to ensure an approximate 1:1:1 balance between the three arms. Randomization codes will be assigned at baseline visit sequentially within each center as patients become eligible for randomization by an independent organization not involved in study conduction. Once a block is exhausted, the next available block will be allocated to a center upon the next randomization.

Blinding
The blinding is ensured by using single-blind technique. A two-operator (treating and assessing) model is used to assist with study masking. The treating operator at each site is **not blind** to intervention arm and he/she is responsible for evaluating patient eligibility, for explaining how to use the devices and for recording and managing AEs. The assessing operator is an independent neuropsychologist or physiotherapist who is **blind** to intervention arm and he/she is exclusively responsible for on-study assessments.

Study discontinuation and drop-out
Patients who are screened for enrolment, but not randomized (e.g. because they do not fulfill eligibility criteria or do not provide a valid inform consent) will be considered as **screening failure** and their data will be not analyzed.
Patients are free to discontinue any intervention at any time, without prejudice to further treatment or care. A patient who decides to discontinue whatever training protocol will be considered as **drop-out** and he/she will always be asked about the reason(s) for discontinuation and the presence of any AE. Premature discontinuation of whatever training protocol does no impact on the patient's participation in the study, since the patient will always be asked to continue attending the subsequent study visit to ensure complete data for an intention-to-treat analysis.
If the patient does not agree to continue in-person study visits, he/she will be considered as **lost to follow-up** and a modified follow-up must be arranged via telephone contact to ensure at least the collection of safety information.

STUDY PLAN AND TIMING OF PROCEDURES

Visit	Week 0 Screening Randomization Baseline	Week 8 (+/- 5 days) Immediate post-training	Week 16 (+/- 5 days) Study Termination
Signed informed consent	X		
Eligibility criteria	X		
Demographic and clinical data collection (CRF)	X		
EDSS score	X		
BDI	X		
MMSE	X		
Randomization & study code assignment	X		
CRIQ	X		
HLAQ	X		
TCI	X		
BICAMS (including SDMT, CVLT2, BMVT-R)	X	X	X
SCWT	X	X	X
2MWT (single-task & dual-task)	X	X	X
Static posturography (single-task & dual-task)	X	X	X
MSIS-29	X	X	X
MFIS	X	X	X
WPAI:MS	X	X	X
Physical activity data collection (actigraph)		X	X
Check of adherence to intervention protocol		X	
Check of AEs		X	X
Device for intervention	Dispense	Return	
Patient diary	Dispense	Return	
Logbook	Dispense	Check	Return
Actigraph	Dispense	Check	Return

Phone contact are planned every two weeks to encourage patients to perform the training and to remind them to complete the patient diary and logbook throughout the study period.

Recruitment and randomization (Baseline visit)
Consenting patients are assessed to ensure they are eligible for the study, i.e. meet all inclusion criteria and none of the exclusion criteria. Patients who are not eligible must not be randomized in the study.

The following procedures will occur during the baseline visit:

- Obtain signed informed consent before any study-related procedure;
- Confirmation of patient eligibility (screening for clinically relevant depression and overt dementia by administering the BDI-II and MMSE, respectively);
- Randomization via computer-generated random numbers;
- Assignment of an individual five-digit code (XX-XXX), with the first two digits identifying the site (01: Rome, 02: Moncrivello, 03: Milan; 04: Genova; 05: Cardiff) and the last three digits deriving from the six-block randomization list;
- Dispensation of device for intervention and relative instructions;
- Dispensation of patient diary (AEs and accidental falls);
- Dispensation of logbook (adherence to intervention);
- Dispensation of actigraph and relative instructions;
- Collection of demographic and clinical data in the case report form (CRF);
- Neurological examination with EDSS score;
- Administration of BICAMS, including the SDMT, CLVT2, and BVMT-R, and SCWT;
- Administration of 2-Minute Walking Test (2MWT) in single-task and dual-task condition;
- Static posturography assessment in single-task and dual-task condition;
- Administration of questionnaires:
  - Cognitive Reserve Index questionnaires (CRQ)
  - Historical Leisure Activity questionnaire (HLAQ)
  - Temperament and Character Inventory (TCI)
  - 29-item Multiple Sclerosis Impact Scale (MSIS-29)
  - 21-item Modified Fatigue Impact Scale (MFIS-21)
  - Work Productivity and Activity Impairment:Specific Health Problems (WPAI:MS).

End of intervention period (Week 8 visit)
The following procedures will occur during the Week 8 visit:

- Return of the device;
- Check of the patient diary for AEs, including accidental falls;
- Return of the logbook;
- Double-check of the logbook and patient diary for adherence;
- Collection of data from actigraph (physical activity);
- Administration of BICAMS, including the SDMT, CLVT2, and BVMT-R, and SCWT;
- Administration of 2MWT in single-task and dual-task condition;
- Static posturography assessment in single-task and dual-task condition;
- Administration of questionnaires:
  - 29-item Multiple Sclerosis Impact Scale (MSIS-29)
  - 21-item Modified Fatigue Impact Scale (MFIS-21)
  - Work Productivity and Activity Impairment:Specific Health Problems (WPAI:MS).

End of study (Week 16 visit)
The following procedures will occur during the Week 16 visit:

- Return of patient diary;
- Check of the patient diary for AEs, including accidental falls;
- Return of actigraph;
- Collection of data from actigraph (physical activity);
- Administration of BICAMS, including the SDMT, CLVT2, and BVMT-R, and SCWT;
- Administration of 2MWT in single-task and dual-task condition;

- Static posturography assessment in single-task and dual-task condition;
- Administration of questionnaires:
  - 29-item Multiple Sclerosis Impact Scale (MSIS-29)
  - 21-item Modified Fatigue Impact Scale (MFIS-21)
  - Work Productivity and Activity Impairment:Specific Health Problems (WPAI:MS).

Unscheduled visits
An unscheduled visit may occur in-between scheduled visits for any reason upon request of the patient or the treating operator, e.g. to deal with problems in using the device, to verify the correct execution of training; to evaluate AE, etc. Phone contact are also planned every two weeks to encourage patients to perform the training and to remind them to complete the patient diary and logbook throughout the study period.

STUDY ASSESSMENTS

Efficacy
Primary endpoint: the SDMT is a measure of sustained attention and information processing speed that has been reported as an easy and quick tool to detect cognitive dysfunction in everyday clinical setting [26],[27], and is more valid and reliable over time than other tests, such as the Paced Auditory Serial Addition Test (PASAT) [35]. The SDMT presents a series of nine symbols, each of which is paired with a single digit, labelled 1 to 9, in a key at the top of a sheet. The remainder of the page has a pseudo-randomized sequence of the symbols and the subject must respond with the digit associated with each of these as quickly as possible. The score is the number of correct answers in 90 seconds. The SDMT scores will corrected by educational level as recommended elsewhere [31].

Secondary endpoint: the BICAMS is recommended by an expert consensus committee of neurologists and neuropsychologists as a brief, practical and universal assessment tool for cognitive impairment in MS. The battery takes 15 minutes to complete, requires no specialist equipment and no specialist expertise in cognitive assessment. The BICAMS includes tests of mental processing speed (SDMT), verbal memory (CVLT2) and visual memory (BVMT-R). The SCWT is also included since the BICAMS does not assess some aspects of executive function. The SCWT evaluates the ability to elaborate relevant and irrelevant dimensions in parallel and to inhibit an automatic response while performing a task based on conflicting stimuli. The procedure comprised of three trials: (i) read a list of words indicating colours printed in black ink as quickly as possible; (ii) name the colour of strings of dots as quickly as possible; (iii) name the colour of the ink of words indicating conflicting colours as quickly as possible (interference condition) [30].

Additional endpoints: we estimate the magnitude of CMI by performing dual-task experiments for walking and balance. For walking, patients will be asked to perform the 2MWT in isolation without any interference (single-task condition) [36] and then to repeat the 2MWT while performing an auditory analog of the Stroop test simultaneously (dual-task cost) [37]. The difference in time spent to perform the 2MWT (dual-task *minus* single-task condition) will be calculated as dual-task cost of walking [38].
For balance, patients will be asked to maintain their balance for 30 seconds as steady as possible on a force platform recording their postural sway (static posturography) while visually focusing on a dot in front of them (single-task condition) [39]; and then to repeat the static posturography assessment while performing the SCWT [40]. The difference in postural sway (dual-task *minus* single-task condition) will be calculated as dual-task cost of balance [38].

We will minimize practice effect related to multiple assessment in two ways: (i) multiple pre-baseline testing to reduce inter-individual and intra-individual variance due to subjects not fully understanding task demands [41]; (ii) administration of alternate versions that are available for serial assessments [42].

Exploratory endpoints: the MSIS-29 is a self-administered questionnaire measuring physical and psychological impact of MS from the subject's perspective; it has been reported to be more sensitive than other quality of life scales in detecting rehabilitation-induced changes [43]. The MFIS-21 is a self-administered questionnaire based on items derived from interviews with subjects with MS concerning how fatigue impacts their lives; it comprises three subscales (physical, cognitive, and psychosocial functioning) [44].The WPAI:MS questionnaire measures employment status, absenteeism, impairment during work, overall work impairment and daily activity impairment [45].

Adherence

All eligible patients will receive a logbook to daily record the log of training (including time and type of game played). The logbook will be given at baseline visit and will be returned to the treating operator at the end of the training period (Week 8 visit). The machine log included in all the devices used in the present study allows double-check of adherence to intervention protocol.

Safety

Patients will be encouraged to contact the treating operator or another component of the study team (excluding the assessing operator) in case of AEs, for any question regarding the study protocol or technical problems. All eligible patients will receive a patient diary to record any AE occurring during the study and the occurrence of accidental falls, defined as an unexpected contact of any part of the body with the ground that not results from loss of consciousness. The patient diary will be given at baseline visit and will be returned to the treating operator at the end of the follow-up period (Week 16 visit).
AEs will be reported according to the World Health Organization (WHO) guidelines for Good Clinical Practice (GCP) in biomedical research on human subjects [46]. AEs are graded as mild (minimal or no treatment required and no interference with daily living activities), moderate (may require treatment and cause some interference with functioning), severe (systemic drug or other treatment required, interruption of daily living activities), or life-threatening (immediate risk of death).

Predictors of outcomes

The TCI, CRIQ and HLAQ will be administered at baseline to explore whether individuals' personality dimensions and pre-morbid motor and cognitive reserve can predict motivation and adherence to intervention, as well as the magnitude of its effects, according to the postulate that individual differences in the cognitive processes or neural networks allow some people to cope better with brain damage.
The TCI is a 240-item self-report inventory that provides scores describing four temperaments, namely Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence; and three characters, namely Self-Directedness, Cooperativeness, Self-Transcendence. The TCI is based on a psychobiological model that attempts to explain the underlying causes of individual differences in personality traits [47]. Patients with MS exhibited higher harm avoidance and lower self-directedness scores than the general population, although these differences disappeared after controlling for depression [48]. In this study, we used a reduced 56-item version developed by Adan A and colleagues (Personality and Individual Differences 2009; 46: 687–692).
The CRIQ is an interviewer-administered questionnaire which includes some demographic data (date and place of birth, gender, place of residence, nationality, marital status) and 20 items grouped into three sections, education, working activity, and leisure time, each of which returns a subscore [49]. Higher CRIQ scores seems to have a protective role in preserving cognitive functions, moderating the effect of MS-related structural damage on cognitive performance [50].
The HLAQ is an interviewer-administered assessment of leisure time physical activity during discrete life periods (e.g., 12–18, 19–34, 35–49, and =50 years of age) [51]. We only will include data from the life periods before the confirmed diagnosis of MS [52]. Higher HLAQ scores seems to be associated with slower MS-related disability progression [52].

INTERVENTIONS

All eligible patients will be submitted to a **8-week training consisting of five 30-min sessions per week** self-administered at home (total number of sessions: 40; total time spent for training: 1,200 minutes).
All the devices will be dispensed free of any charge for patients. However, all the devices must be returned to the study team at the study termination or in case of premature study discontinuation.

Exergames (intervention of interest)
The training protocol will be delivered by the Nintendo ® Wii balance board and consists of repetitions of several games selected from the "Wii Fit Plus" package (http:// www.wiifit.com/training/balance-games.html). Each game starts at basic level, and when a certain score is reached, patients is automatically transferred to a more advanced level. Patients will be encouraged to play the next game if they have a level progress; otherwise, 10 minutes will be allocated for each game. During the first 4 weeks of training, patients will be allowed to play only "Zazen" (sitting position), "Table Tilt" and "Ski Slalom"; thereafter they will add the remaining games "Penguin Slide", "Tightrope Walk", "Balance Bubble" and "Soccer Heading" [9].

Adaptive COGNI-TRAcK (comparator intervention)
The training protocol will be delivered by a dedicated app for mobile devices (mobile phone or tablet). The app implements three different types of exercises (each one executed for about 10 min a session), consisting in a visuo-spatial working memory task, an "operation" N-back task and a "dual" N-back task. The adaptive training is structured so that the exercises difficulty level will increase by one step every time the user will perform a correct exercise. On the other hand, the difficulty level will decrease by one step if the exercise is incorrect for three times in a row [24].

Sham COGNI-TRAcK (placebo-analogue intervention)
The training protocol will be delivered by a dedicated app for mobile devices (mobile phone or tablet) as previously described for adaptive COGNI-TRAcK [24]. However, the non-adaptive training (placebo-analogue intervention) consists in an algorithm implementing two low difficulty levels alternating every day regardless of the user's performance.

Concomitant medications
Patients are encouraged to continue his/her disease-modifying treatment (DMT) and symptomatic treatments without change in dosage or administration frequency throughout the entire study period. Any change in pharmacological treatment, including DMT, during the study must be recorded. As per eligibility criteria, patients who change any medication over the previous 3 months should be not enrolled.

Forbidden treatments and interventions
No pharmacological treatment is strictly forbidden; however, patients are encouraged to not start pharmacological treatments that can potentially impact on cognition, namely antidepressants, dalfampridine, nabiximols, modafinil, amantadine, dopamine-agonists.
Steroid administration due to MS relapse or any symptomatic drug initiation due to any MS-related symptom should be considered as an AE.
Patients are encouraged to not start any other type of physiotherapy or rehabilitation during the study period, but they are encouraged to continue his/her physiotherapy or rehabilitation program if started at least 3 months before the study enrolment.

STATISTICAL PLAN

Sample size estimation
Overall, we will randomize **126 patients** (considering even a 20% drop-out rate), based on two previously published studies that have found:
(i) a significant effect of an home-based cognitive training using the Dr. Kawashima Nintendo ® Brain Training that promoted an about 8-point mean increase at SDMT score (with respect to wait-list group) [53];
(ii) a significant effect of adaptive COGNI-TRAcK that promoted an about 8-point mean increase at SDMT score (with respect to a sham intervention) [24];
(iii) a 50%-difference in proportions of responders (10/14 versus 3/14 in adaptive COGNI-TRAcK group and sham COGNI-TRAcK group, respectively) [24], according to a responder definition of SDMT change approximating 4 points or 10% in magnitude [28].

For the non-inferiority comparison, the null hypothesis is that the intervention with exergames is inferior to adaptive COGNI-TRAcK, while the alternative hypothesis is that the intervention with exergames is non-inferior to adaptive COGNI-TRAcK by a pre-defined amount of SMDT score.
If there is truly no difference between exergames and adaptive COGNI-TRAcK, then 35 patients per arm are required to ensure, with a statistical power of approximately 85%, that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the predefined non-inferiority margin of 8-point change in SDMT.

For the superiority comparison, the null hypothesis is that the intervention with adaptive COGNI-TRAcK is not superior to sham COGNI-TRAcK, while the alternative hypothesis is that the intervention with adaptive COGNI-TRAcK is superior to sham COGNI-TRAcK in increasing the proportion of responders as afore defined. Enrolling 35 patient per arm will ensure a more than 95% power in detecting a statistical significance between-group difference of 50% at two-sided alpha level of 5%.

Statistical analysis
All analysis will be based on the intention-to-treat principle using the fully analysis dataset including all randomized patients. Missing data will be handled by multiple imputation method, with the assumption that some data will be missed completely at random.

Efficacy analyses: efficacy data will be analyzed by parametric and/or non-parametric Repeated Measures Analyses of the Variance (RM-ANOVAs) with effect size estimation. In each analysis, we will consider as dependent variable all measures or score derived from study assessments; the three study visits (Baseline, Week 8 and Week 16) as within-subject factors; and intervention arms (exergames, adaptive COGNI-TRAcK and sham COGNI-TRAcK) as between-subject factors. Effect sizes will be estimated as Cohen's F-squared, rated as small, medium, and large for values of 0.02, 0.15, and 0.35, respectively [54].
Safety data regarding time to first accidental falls will be analyzed as time-to-event data by Kaplan-Meier curves and Log-Rank test with a factor for intervention arms.

Safety analyses: data regarding the occurrence of adverse events during the intervention period and the follow-up period will be analyzed by the Chi-squared test comparing the independent distribution of events according to intervention arms.

Predictors of outcomes: logistic regression analyses will test if the achievement of a clinically relevant change in the pre-planned endpoints is predicted by scores derived from CRIQ, HLAQ and TCI, after controlling for a set of baseline covariates including sex, age, disease duration, EDSS score, performance on the explored task. For those endpoints lacking of a definition of clinically relevant change, we will adopt Analyses of Covariance (ANCOVAs) with immediate post-training score as dependent variables, intervention arm as fixed factor and a set of baseline covariates including sex, age, disease duration, EDSS score, baseline performance on the explored task, as well as scores derived from CRIQ, HLAQ and TCI as covariates of interest.

Pre-planned statistical significance level
Exergames and adaptive COGNI-TRAcK will be compared with sham COGNI-TRAsK as placebo-analogue arm. Therefore, all analysis will be corrected with Bonferroni adjustment for multiple comparisons of two-sided tests, giving a two-sided significant p-value of 0.025.

Interim analysis
An interim analysis will be conducted when at least 50% of the estimated sample size will complete the 8-week intervention period.

STUDY GOVERNANCE AND OVERSIGHT

Steering committee
The steering committee shall comprise the Principal Investigator (PI) and all the co-investigators reported in this study protocol.
The steering committee will be responsible for the overall design, interpretation, supervising and reporting (presenting at national and international congresses and publishing in peer-reviewed journals). Members of steering committee will be also responsible for providing clinical guidance on study implementation and conduct in their respective sites.

Data Monitoring
An independent Data Monitoring Committee (DCM) will be appointed to review the overall conduct of the study, with particular attention to eligibility criteria, randomization, and collection of efficacy and safety data. The DCM will have access to the individual treatment codes while the study is ongoing; therefore, if DMC expresses safety concerns, appropriate information will be sent to the PI, regulatory authorities and study funder Associazione Italiana Sclerosi Multipla (AISM).
The DCM is also responsible for ensuring the maintenance of blinding and integrity of the study.

ETHICAL AND REGULATORY REQUIREMENTS

Ethical conduct of the study
This study will be performed in accordance with specific national laws and the ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments.
Ethical principles adopted in this study are consistent with International Conference on Harmonization/GCP applicable to biomedical research on human subjects [46] and with the FISM ethical code (provided as appendix).
There is no incentive for patients who participate in the study.
In no way this study will interfere with the standard care offered to patients with MS in each involved sites, in particular regarding scheduled or unscheduled outpatient activities, including clinical, laboratory and MRI follow-up and management of DMT or any symptomatic treatment.

Informed consent and patient data protection

The Institutional Ethic Committee (IEC) of the PI site should approve the final version of the study protocol, informed consent form and any other written information and/or materials provided to patients recruited in this study. The PI is responsible for the distribution of these documents to the lead IEC and, once obtained the approval, to the other applicable IEC and to the staff of all study sites.

The PI and co-investigators at each site will ensure that:

- each patient is given full and adequate oral and written information about the nature, purpose possible risk and benefit of the study;
- each patient is notified that they are free to discontinue from the study at any time, without prejudice for further treatment or care;
- each patient is given the opportunity to ask questions and allowed time to consider the information provided;
- the original signed inform consent form is stored in the study file at site;
- a copy of the signed consent form is given to the patient.

The informed consent form will incorporate wording that complies with relevant data protection and privacy legislation.

Insurance

Even if the present research does not encompass any pharmacological or surgical intervention, and even if neither exergames nor COGNI-TRAcK are associated with relevant AE or side effects (see also the paragraph “Risk:benefit ratio and ethical consideration”), we will stipulate an insurance policy to grant specific cover in connection with the reimbursement of damages caused to the subjects by the study activities throughout the entire duration thereof, thus covering any civil liability of investigator and sponsor of the clinical trial, without excluding any damage which may be unintentionally caused by accident and/or be attributed to negligence, imprudence or inexperience.

PI and co-investigators will inform the participants to the study protocol, even through the informed consent, that the insurance policy covering damages caused by civil liability (as third part liability) in the study will not cover any amount exceeding its limit of liability and that such policy exclusively applies to damages for which a claim was submitted within and not later than the period provided in the policy. This restriction shall not in any event impair the right of the damaged party to seek reimbursement of damages from the person liable therefor. Insurance shall cover death, all permanent and/or temporary impairment of health conditions, relevant financial consequential losses which are the direct consequence of the study and which can be traced to the liability of all people operating for the performance of the study.

Audits and inspections

Authorized representative of regulatory authority, IEC or AISM/FISM may perform audit or inspections at any site, including source data verification. The reference Institution/Hosting Organization shall ensure due collaboration to allow such meetings and visits to take place. Participation in the progress and final report meetings organized by AISM/FISM is required per each annual period of the duration of the project and for the year following the closure of the project.

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APPENDICES

1. CRF
2. BICAMS (SDMT, CVLT2, BVMT-R)
3. MSIS-29
4. MFIS-21
5. WPAI:MS
6. HLAQ
7. CRIQ
8. TCI
9. Patient diary
10. Logbook
11. Ethical code FISM
12. Informed consent form