


# Improving cognition in people with multiple sclerosis: study protocol for a multiarm, randomised, blinded trial of multidomain cognitive rehabilitation using a video-serious game (E-SEP cognition)

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**To cite:** Lenne B, Degraeve B, Davroux J, *et al.* Improving cognition in people with multiple sclerosis: study protocol for a multiarm, randomised, blinded trial of multidomain cognitive rehabilitation using a video-serious game (E-SEP cognition).

*BMJ Neurology Open*

2023;5:e000488. doi:10.1136/bmjno-2023-000488

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjno-2023-000488>).

Received 03 July 2023

Accepted 15 October 2023



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## ABSTRACT

**Introduction** Multiple sclerosis (MS) is a prevalent neurological disease characterised by disseminated areas of demyelination and atrophy within the central nervous system, inducing cognitive disorders in 45%–65% of persons with MS (PwMS). Neuropsychology and neuroimaging studies provide evidence of the effectiveness of cognitive rehabilitation interventions, including memory and attention. Recently, serious game therapy (SGT) has been used in rehabilitation to improve cognitive processing speed. The aim of this study is to describe the protocol of a randomised controlled trial (RCT) to test the efficacy of a tablet-based cognitive home intervention among ambulatory PwMS, in comparison to a standardised neuropsychological rehabilitation.

**Methods and analysis** This will be a parallel-assignment, double-blinded, RCT. One hundred and fifty (75 per arm) PwMS will be randomly assigned to receive cognitive rehabilitation session over 4 months (four 20-min sessions/week) of either: (1) tablet-based SGT or (2) conventional cognitive exercises. The same assessor will evaluate outcome measures at three points: at baseline (T0), after the 16 therapy sessions weeks (T1), and 6 months after the end of treatment (T2). The primary outcomes were the scores from the *Brief International Cognitive Assessment for Multiple Sclerosis* (BICAMS). Data analysis will be performed to compare the efficacy of the two treatments. We expect superior efficiency of tablet-based SGT in contrast to conventional cognitive exercises, based on BICAMS measures of speed processing information and episodic memory.

**Ethics and dissemination** The trial protocol is registered on ClinicalTrials.Gov (NCT04694534) and benefits from a favourable opinion from an ethics committee (RC-P0066-2018-A00411-54).

## INTRODUCTION

Multiple sclerosis (MS) is a prevalent neurological disease characterised by disseminated

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Cognitive dysfunction is prevalent in multiple sclerosis (MS), affecting up to 70% of patients, encompassing deficits in information processing speed, memory and executive functions.
- ⇒ Despite an accumulation of promising neuropsychological and neuroimaging outcomes of the efficiency of cognitive rehabilitation interventions, there is a lack of validated and widely accepted clinical procedures among persons with MS (PwMS).
- ⇒ Video game technology could be used as a treatment tool in rehabilitation, given its low cost, high portability and fun, challenging and self-motivating, which are critical elements for successful rehabilitation.

## WHAT THIS STUDY ADDS

- ⇒ Randomised controlled trial (RCT) assesses the efficiency of a home tablet-based intervention specifically developed for PwMS and adapted to their specific cognitive impairment.
- ⇒ This RCT assesses the efficacy of this device on cognitive functioning and measures reflecting the transfer of benefits to everyday cognitive function.
- ⇒ Long-term benefits of therapy are assessed (6-month follow-up).

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This programme offers a cognitive remediation method for PwMS, using a home-based programme reaching patients in widely dispersed areas where accessibility constraints occur.
- ⇒ This cognitive intervention provides playful activities, therefore less stigmatising and time-consuming.
- ⇒ Making the rehabilitative session more engaging for patients may increase involvement and adherence in the rehabilitation process.

areas of demyelination and atrophy within the central nervous system,<sup>1,2</sup> inducing a broad range of symptoms. Among these symptoms, cognitive impairment occurs in 45%–65% of persons with MS (PwMS) and seems to appear early and independently of other clinical features of the disease (such as disease duration or level of disability).<sup>3</sup> MS-related cognitive impairment is mainly characterised by slowed information processing speed (IPS), as well as working memory, episodic memory and executive functions deficits.<sup>3</sup> Cognitive impairment is one of the invisible symptoms of MS, which is associated with depression, unemployment, reduced social interaction, inability to drive and compromised quality of life (QoL).<sup>4,5</sup>

Currently, management of cognitive impairment involves two approaches: pharmacological and behavioural.<sup>6</sup> To date, there is limited support for the efficacy of pharmacological treatments (ie, disease-modifying treatments and symptomatic therapies) for MS-related cognitive impairment.<sup>6,7</sup> The most common behavioural approach for managing cognitive impairment in MS involves cognitive rehabilitation. There is an accumulation of neuropsychological evidence to the efficiency of cognitive rehabilitation interventions, especially for memory and attentional disorders,<sup>8–11</sup> also supported by neuroimaging outcomes.<sup>12,13</sup> Recently, a meta-analysis on efficacy of computerised cognitive training, including a total of 20 RCTs encompassing 982 participants (mainly with relapsing-remitting MS) was carried out. With different study designs and rehabilitation methodologies, computerised cognitive training involves small to moderate effect sizes for attention/processing speed, executive functions, and verbal and visuospatial memory, contrasting with inconclusive effect on working memory, fatigue, and psychosocial and daily functioning.<sup>10</sup> In recent years, video game technology has begun to be used as a treatment tool in rehabilitation, given its low cost, high portability, off-the-shelf nature and ability to deliver engaging, highly repetitive, task-oriented, standardised, active-learning therapies.<sup>14</sup> Recently, gaming consoles introduced in clinical and research settings may represent a low-cost opportunity of delivering virtual-reality training. In this line, De Giglio et al., 2015<sup>15</sup> evaluate the effectiveness of a home-based cognitive rehabilitation programme based on the video game Dr Kawashima's Brain Training, in improving attention, IPS, and working memory of PwMS. Compared with waitlist control, PwMS submitted to an 8-week home-based cognitive rehabilitation programme showed a significant improvement of IPS, correlated to an increased functional connectivity (FC) in the cingulum, precuneus and bilateral parietal cortex and a lower FC in the cerebellum and in left prefrontal cortex. In addition, PwMS have defined gaming experience as fun, challenging and self-motivating, which are critical elements for successful motor learning.<sup>16</sup> Finally, patients' motivation seems to increase during video game rehabilitation, allowing patients to exercise more consistently.<sup>17</sup>

In a more specific way, Bove et al., 2021<sup>18</sup> recently proposed a videogame-like application, specifically targeting the remediation of IPS. This in-home digital intervention, in comparison to non-specific video games (not involving cognitive functions impaired in PwMS), resulted in substantial and durable improvements in processing speed. If Symbol Digit Modalities Test (SDMT) z-scores indeed increased in both (intervention and control) groups, only the intervention group showed long-term improvements by maintaining a clinically meaningful 4+-point increase in SDMT above their baseline after another 8 weeks of observation. A previous feasibility study underlines the right adhesion to this treatment, with a completion of 75% of prescribed sessions in 78% of participants and a completion of all sessions in 50% of them.<sup>19</sup>

Despite promising research efforts, there is a lack of validated and widely accepted clinical procedures for cognitive neurorehabilitation among PwMS. Development of such procedures should be inspired by cognitive neuroscience, composed of conventional neuropsychological training and cognitive behavioural therapy as well as therapeutic video games. Subsequently, large-scale validation will be needed with meaningful outcome measures reflecting the transfer of benefits to everyday cognitive function and the maintenance of training effects.

## AIMS

This study aims to test the efficacy of a tablet-based serious game therapy (SGT) on cognitive functioning in ambulatory PwMS, in comparison to a standardised neuropsychological rehabilitation (SNT).

We hypothesise that features of tablet-based SGT will increase the cognitive benefit of the rehabilitation therapy, together with enhancement treatment adherence and motivation.

## METHODS AND ANALYSIS

### Study design and setting

This study is a multicentre, multiarm, blinded, randomised, controlled trial, which includes three assessments points: at baseline (T0), after the 16 therapy sessions weeks (T1), and 6 months after the end of treatment (T2). The outcome assessor and the statistician 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 SGT or the SNT. Subjects will be recruited from the patient afferent to outpatient neurological and rehabilitation clinic at six different university hospitals. Patient recruitment started on 8 October 2021, and it is going to finish on 8 April 2025. Each site has at least one blinded and one unblinded research assistant. The blinded measurement assessor (neuropsychologist) will perform all cognitive assessment (baseline, 4-month and 10-month testing). The unblinded research assistant will

screen potential participants. If a participant meets the inclusion criteria (see below), the unblinded research assistant is responsible for randomising participants using CleanWeb. As the study design aims to mask the intent of the intervention given to the participants, the unblinded research assistant will be strictly instructed not to discuss participant allocation and participants will likewise be instructed not to reveal details that can indicate their group allocation to the blinded assessor.

The trial protocol has been registered on ClinicalTrials.gov (NCT04694534) and benefits from a favourable opinion from an ethics committee for the protection of people involved in an interventional clinical trial (RC-P0066-2018-A00411-54).

### Selection criteria and recruitment of participants

People affected by MS (according to the 2010 McDonald criteria<sup>20</sup>) will be included if they meet the following inclusion criteria:

- ▶ Men and women, aged 18–65 years old.
- ▶ Diagnosis of MS (primary or secondary progressive, relapsing–remitting), without relapses in the preceding 6 weeks.
- ▶ Cognitive complaint and Cognitive deficit of at least one of the 3 Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) scores ( $z < -1.5$ ).

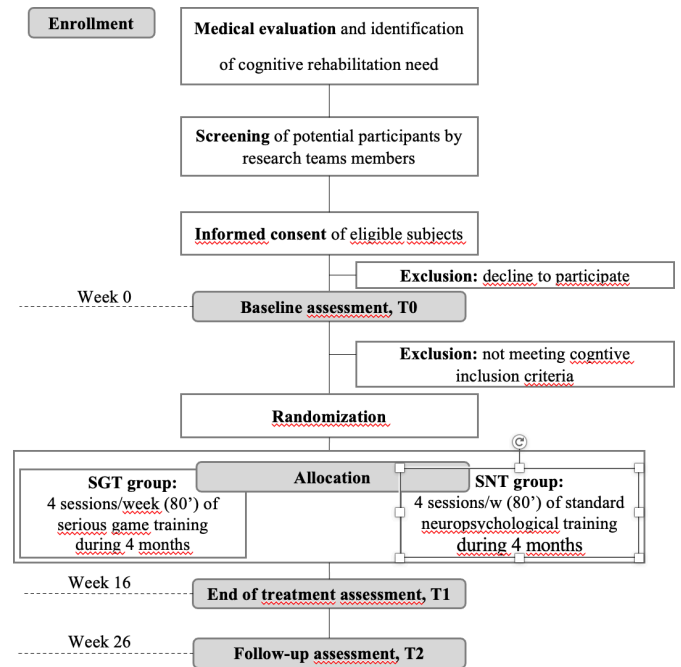
Exclusion criteria will be:

- ▶ Nervous breakdown (Fast-Beck Depression Inventory > 10).
- ▶ Other neurological or psychiatric conditions which may affect cognitive functions.
- ▶ Severe visual impairment limiting the performance of the cognitive assessments and use of the tablet.
- ▶ Other medical conditions which 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. In the case that they are interested in taking part in the study, the physician will give them a letter explaining the study's purpose and procedures, time commitments, risks, potential benefits, treatment alternatives, study staff contact information and the consent form. After a few days of reflection, the potential participant will be contacted. If the subject decides to take part in the study, the research staff will give him/her an appointment for instructions in signed the consent form and to explain the baseline outcome measures, conducted by a neuropsychologist. 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 guidelines (figure 1).

### Randomisation and blinding

The selection of eligible patients is made by the medical team, and the randomisation of the selected patient



**Figure 1** Consolidated Standards of Reporting Trials flow diagram of the study (all images have been created by authors). SGT, serious game therapy; SNT, standard neuropsychological treatment.

(meeting inclusion criteria) will be carried out by a clinical research associate. Patient will be randomised to one of the two treatment groups through a randomisation approach (1:1 ratio). The randomisation scheme will be generated using the CleanWeb site to prevent selection bias. The neuropsychologist assessor will be blinded concerning the subject's group allocation. All outcome data and assignment groups will be organised in different data sets 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 'European Union Data Protection Directive (95/46/EC 24 October 1995).

### Intervention

In each condition, patients will receive medical and paramedical care according to National Health Authority guidelines. In addition, they will receive specific instructions for cognitive rehabilitation, which will take place during the next 4 months following inclusion in the study, 4 sessions of 20 min of effective activity per week. Each cognitive training session is carried out at home, with at least 24 hours between sessions.

### Serious Game Therapy

The SGT is a home-based videogame developed by a multidisciplinary team, including neuropsychologists and a physical medicine physician, and programmed by the company '3 Prime' between 2018 and 2020. The SGT, accessible via a secure dedicated, was realised using a touch screen, from a first-person perspective. The SGT is a serious ecological game based on a virtual vacation

island (*Cognition Island*), in which subjects are invited to interact with different parts of the scenario and perform specific tasks. All actions performed by subjects in the SGT are recorded and measured during the completion of different tasks, involving different cognitive functions, divided into four worlds, with a specific goal, involving specific cognitive functions: (1) world 1: planning, (2) world 2: episodic memory, (3) visuospatial processes and (4) divided attention. Each of these worlds comprises different tasks involving different cognitive processes: episodic memory, working memory, mental flexibility, inhibition, IPS and visuospatial processes. All scenarios are paced in terms of increasing difficulty and have the same structure:

► The beginning of each game session is preceded by a phase of presentation of one or two specific cognitive function(s), their characteristics, their operation and the consequences of their dysfunction, to improve metacognition and understanding of cognitive functioning.

► A main objective in the game, involving different cognitive functions.

► Additional activities, involving a main cognitive function.

For example, in the second world, entitled 'Boat trip', the patient organises a trip out to sea. This scenario is preceded by a presentation of cognitive functions: episodic memory and inhibition. During this scenario, the patient is required to obtain a boating license (involving episodic memory), carry out driving tests (episodic memory and sustained attention), purchase the equipment needed for the trip (planning, multitasking) and then carry out the boat trip. During the boat trip, the patient explores different islands, involving different working memory tasks.

The passage from one stage to another is done when the patient has obtained a percentage of success for each activity, according to the level of difficulty of the task. Each specific task contains four difficulty levels. During the first exploration of a world, the patient begins each activity at level 1. When this first level is validated, the patient moves on to the next level. During a level, less than 50% performance rate leads to a drop back down to

the lower level (or is maintained at level 1). With a performance between 50% and 75%, the patient is maintained at the current level. Above 75%, the patient goes on to the next level. And so on until the last level. For each activity, the patient also has the possibility of modulating the level of difficulty of the task him or herself to allow the implementation of adapted strategies. To improve meta-cognitive abilities, advice (pop-ups) will be offered to the patient, during all activities and in difficult situations. The unlocking of the bonus worlds is underpinned by the repetition of the mini-games and the realisation of the activities within the scenarios. This repetition is encouraged by earning rewards when performing the activities. For each task performed, the patient receives feedback on the level of his or her performance. If performance levels fluctuate from one session to the next, patients are offered explanations on the variables that may explain these fluctuations, to improve their understanding of cognitive functioning. The overall structure of the serious game is shown in figure 2. Screenshots of the game are provided in online supplemental data 2.

### Standardised neuropsychological rehabilitation

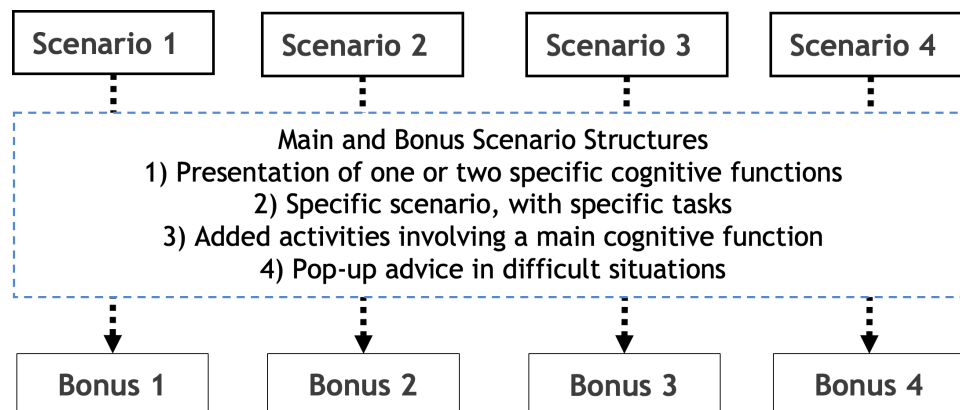
The standardised cognitive remediation procedure consists of different paper-and-pencil cognitive activities involving cognitive functions weakened in PwMS (such as learning and attentional abilities). Patients are provided with cognitive stimulation booklets. Each of these booklets features different activities such as sudoku, memory games, word games and explorations games, with a real cognitive challenge but without the motivational and playful characteristics of the serious game.

### Concomitant care and recommendations

All the subjects will be advised not to undertake other cognitive rehabilitation until the end of the assessment period.

### Intervention fidelity and monitoring of adverse events

Any unpredictable adverse events will be recorded in the patient's registry and the electronic study database. Their



**Figure 2** Global structure of the serious game therapy (all images have been created by authors).

**Table 1** Schedule of enrolment, interventions and assessments

	Study period			
	Enrolment	Allocation	Post treatment	Close-out
Time point	T-1	T0	T1	T2
Eligibility screen	×			
Informed consent	×			
Allocation		×		
Interventions				
Serious game		↔		
Standard		↔		
Primary outcomes		×	×	×
Secondary outcomes		×	×	×
T-1 enrolment, T0 before treatment, T1 4 months after, T2 6-month follow-up.				

management will agree with the related hospital policies, with a referral for appropriate medical follow-up.

### Outcome assessment and data collection

In each medical centre, all the clinical evaluations will be performed by the same blinded assessor at the three time-point evaluations: (T0) baseline, before the first intervention; (T1) end of treatment, after the 16 weeks of therapy sessions; (T2) follow-up, 6 months after the end of treatment. Demographical, clinical and neuropsychological assessment will be delivered by a physician and a neuropsychologist adequately trained in evaluation procedures. A summary of the study plan is reported in [table 1](#).

The following clinical and demographic data will be collected by an interview preceding the experiment: age, sex, years of education, laterality, medical history, MS subtype, disease duration, date of the last relapse and current disease-modifying treatment. Physical disability will be assessed using Expanded Disability Status Scale (EDSS).<sup>21</sup>

### Primary outcome measures

The primary outcomes were the measures from the BICAMS.<sup>22</sup> Due to its excellent psychometric properties, the BICAMS has been introduced as an international consensus instrument to screen cognitive status in PwMS<sup>23</sup> and this battery has been standardised for the French population.<sup>24</sup> The BICAMS includes three cognitive measures: The *California Verbal Learning Test*,<sup>25</sup> the *Brief Visuo-spatial Memory Test*<sup>26</sup> and the *SDMT*<sup>27</sup> ([table 2](#)). Details on description and measures of each test are reported in the additional document (online supplemental data 1).

### Psychological assessment

Cognitive assessment is completed by psychological assessment, notably Subjective cognitive decline by the McNair & Kahn scale,<sup>28</sup> depression by the *Fast-Screen Beck Depression Inventory (BDI-FS)*,<sup>29</sup> anxiety by *State Trait Anxiety Inventory (STAI-Y)*<sup>30</sup> and fatigue by a *Visual Analog Scale (VAS) of Fatigue* ([table 2](#)). Details on the description of each psychological assessment are reported in the additional document (online supplemental data 1).

### Data management

Data analysis will be performed according to the research hypothesis mentioned, using the SPSS V.25.0 (SPSS).

### Sample size and power

The main objective of this study is to compare the effectiveness of rehabilitation in the two groups. First, the evolution of each BICAMS score between inclusion and the two measurement points will be compared between the two groups using a mixed model. Second, the groups will be compared specifically at each measurement time using an Analysis of Covariance (ANCOVA). The calculation of the number of subjects was based on the ANCOVAs which will be carried out for the three BICAMS tests. A maximum of six tests will be performed; thus, a multiple comparison correction will be used. The number of patients needed for the study has been calculated so that each test has sufficient power, considering the multiplicity correction that will be used. To be relevant, the difference between the two groups must be greater than the minimum clinically important difference (MCID), estimated from the SD and the intraclass correlation coefficient of normative data.<sup>22 23</sup> An ANCOVA being carried out, we can estimate the number of subjects necessary by knowing the correlation between the score after and before the intervention. Indeed, the number of subjects required in an ANCOVA is  $(1-r^2)n$ , where  $n$  is the number of subjects required when using a Student's t-test and  $r$  the correlation between the variable of interest and the covariate. We estimated it by the intraclass correlation coefficient. By taking all these elements into account, in order to be able to detect a difference between the two groups of at least the MCID in one of the BICAMS tests with a power of 90% and an alpha risk of 5%, and considering 20% lost to follow-up, 75 patients must be included per group, that is, a total of 150 patients.

### Statistical analyses

Descriptive statistics (mean and 95% CI) will be reported before treatment, after treatment and at the 6-month follow-up for all the selected variables: the means and SD will be the numbers and frequencies for the qualitative variables.

The comparability of the two groups will be checked for the quantitative data by the Student's t-test in the event of normality or the Mann-Whitney-Wilcoxon test otherwise; for discreet data by the Mann-Whitney-Wilcoxon test; for

**Table 2** Cognitive and psychological assessment

Cognitive assessment	Cognitive functions	Measures
BICAMS CVLT	Verbal episodic memory	Total free recall (/60)
BVMT-R	Visuospatial episodic memory	Total free recall (/12)
SDMT	Information processing speed	Number of correct substitutions
Direct and forward digit spans	Working memory	Level of the span Total number of correct responses
SCWT	Inhibition	Time to complete each condition Total number of errors
TMT	Reactive flexibility	Time to complete each condition Total number of errors
Verbal fluencies	Spontaneous flexibility	Number of different words.
TOL	Planification	Number of movements Latence and total times
MET	Planification	Errors and time to complete
D2	Selective attention	Number of correct items in all trial Number of incorrect responses
PASAT	IPS / working memory	Number of correct responses (/60)
Psychological assessment	Psychological dimensions	
Subjective cognitive decline (SCD)	Cognitive complaints	0–96, with higher score indicating more SCD.
BDI-FS	Depression	0–21
STAI-Y	Anxiety	20–80
VAS	Fatigue	

Other cognitive assessments complement primary cognitive measures. All additional cognitive assessment is listed in [table 2](#). Details on description and measures of each test are reported in the additional document (online supplemental data 1).

BDI-FS, Fast-Screen Beck Depression Inventory; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuo-spatial Memory Test; CVLT, California Verbal Learning Test; MET, Multiple Errands Test; PASAT, Paced Auditory Serial Addition Test; SCWT, Stroop Color-Word Test; SDMT, Symbol Digit Modalities Test; STAI-Y, State Trait Anxiety Inventory; TMT, Trail Making Test; TOL, Tower of London; VAS, Visual Analog Scale.

qualitative data by the  $\chi^2$  test or Fisher's exact test in the event of insufficient numbers.

Analysis of the primary outcome measures: the evolution curves of the difference of the BICAMS tests for each group will be compared by implementing a mixed linear model integrating the group and time as fixed effects. The patients will be integrated in random order to consider the correlation between the data due to the repeated nature of the measurements. The regression application conditions will be checked graphically on the residuals (normality and homoscedasticity). A log transformation may be applied if these conditions are not verified. The significance of the group will be sought as well as that of the Treatment  $\times$  Time interaction. 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. To calculate the effect size of both treatments, we will use Cohen's *d*. Significance will be recognised for  $p < 0.05$ .

### Intention to treat

Every attempt will be made to avoid missing data through a careful check of self-reported measures, such 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 includes a data monitoring committee. An update on trial progress will be shared with the Research office every 6 months. 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 studies on the use of computerised cognitive training in MS.

## DISCUSSION

This trial may highlight the efficiency of home video serious game in the cognitive rehabilitation of PwMS. This study is the first to evaluate the effectiveness of a

serious game, aimed at the global and specific cognitive remediation of PwMS.

Our expectation from the proposed research is to observe a more significant effect from SGT on cognitive disorders in PwMS compared with a conventional and less specific approach. We expect a benefit from the use of this SGT on complaints and cognitive functioning. In addition, due to the focus of this programme on metacognitive ability improvement and the implementation by the patient of compensation strategies (ie, self-modulation of the level of difficulty of the task), we expect a long-term maintenance of the benefits and their generalisation in cognitive domains. Ultimately, this will allow large-scale distribution to PwMS requiring cognitive rehabilitation of a tool which is playful, patients invest in more easily (because less stigmatising), less time-consuming (compared with conventional rehabilitation) and therefore more suitable for patients in professional activity or geographically isolated.

As underlined by Brochet,<sup>8</sup> the evidence of the efficacy of telerehabilitation is still limited but the results encourage further studies in this field. Although a demonstration of the effectiveness of multidomain cognitive rehabilitation, on QoL and transfer to cognitive domains different from those trained, is lacking, several studies show the feasibility of individual cognitive rehabilitation in daily life settings and home telerehabilitation using cognitive computerised training. A meta-analysis by Lampit *et al*<sup>10</sup> underlines that small-to-moderate effect sizes were found for attention/processing speed, executive functions and verbal and visuospatial memory. Nevertheless, computerised training is often repetitive and boring, decreasing patients' interest and the rehabilitation process. Videogames which propose a more playful solution might increase this adhesion. Making the rehabilitative session more engaging for patients may increase involvement and adherence in the rehabilitation process. Increased participation and motivation have already been observed in PwMS treated with gamified training.<sup>31</sup> Moreover, PwMS defined gaming experience as fun, challenging and self-motivating, critical elements for successful motor learning.<sup>16</sup> Active video games may offer an enriched environment useful for subjects with neuropsychological disorders, like attention deficit or impaired alertness. Recently, gaming consoles introduced in clinical and research settings may represent a low-cost opportunity of delivering virtual-reality training. Bove *et al.*, 2021<sup>18</sup> proposed an application as a video game, specifically targeting the remediation of IPS, with encouraging results. Nevertheless, this device targets exclusively the IPS. If this disorder is the most frequent and early deficit in PwMS,<sup>32</sup> executive function, working memory and learning deficits lead to significant limitation in activities of daily living,<sup>33</sup> which justifies the development of more global tools for cognitive rehabilitation among PwMS.

Our study may have several limitations. First, because the frequency of rehabilitation sessions is fixed in both conditions (up to 4 sessions of 20 min per week), this protocol will not address the effects of the intensity of cognitive rehabilitation. We lack a more ecological evaluation of the impact of the treatment, especially since the serious game targets the transfer of benefits to activities of daily living. Only a social participation questionnaire was carried out. Third, we will not use any instrument to assess patients' satisfaction towards the experimental treatment. In the same way, no evaluation of the perception of the efficiency of the tool, apparent validity, will be used. Good apparent validity guarantees patient adherence to treatment. Fourth, no neuroimaging technique will be used to show the possible neuroplastic changes in the brain due to SGT. Finally, we will not study the effects of combined treatment of SGT and other cognitive or motor rehabilitation, despite the fact that combining treatments seems to increase training efficacy and boost effects of a single approach.<sup>17</sup> Further studies should consider these possible limitations and confirm the results related to neuropsychological outcomes.

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**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** No, there are no competing interests.

**Patient consent for publication** Not applicable.

**Ethics approval** The trial protocol has been registered on ClinicalTrials.gov (NCT04694534) and benefits from a favourable opinion from an ethics committee for the protection of people of Nord Ouest IV (RC-0066-2018-A00411-54). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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