Research Protocol

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The effectiveness of combining a home-based Digital motor Telerehabilitation program with conventional therapy in progressive multiple sclerosis: A study protocol for a multicenter, randomized controlled trial

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Abstract

Objective: The primary aim is to evaluate the effectiveness of in-hospital rehabilitation followed by a home-based Digital Telerehabilitation program on mobility versus in-hospital rehabilitation alone in patients with Progressive Multiple Sclerosis. Secondary aims are the intervention's impact on clinical, physiological, psychological, and economic outcomes.

Methods: This multicenter, single-blind, randomized controlled trial will involve 78 participants with Progressive Multiple Sclerosis. All participants will complete 10 in-hospital rehabilitation sessions (1 hour/day, three days/week). The experimental group will receive an additional 12-week home-based Digital Telerehabilitation (3 sessions/week), while the control group general self-management instructions. Based on primary and secondary outcomes, a blinded rater will evaluate participants before and after rehabilitation and at 12 and 24 weeks follow-up.

Results: Integrating home-based Digital Telerehabilitation is expected to mitigate the progression of disability, promote self-management, and reduce healthcare costs, offering a cost-effective and accessible solution for managing Progressive Multiple Sclerosis.

Conclusions: This study will provide essential insights into the role of Digital Telerehabilitation in the hybrid care model to manage Progressive Multiple Sclerosis, with the potential to guide clinical practice and inform health policy. The physiological and economic evaluations will further clarify the benefits and cost-effectiveness of the intervention.

Trial registration: This trial was registered in ClinicalTrials.gov (NCT06485115; URL: https://clinicaltrials.gov/study/NCT06485115?cond=NCT06485115&rank=1).

Keywords

Multiple sclerosis, Telerehabilitation, quality of life, dual task, wearables

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Introduction

Background and rationale

Multiple Sclerosis (MS) is a complex, chronic disease of the Central Nervous System (CNS) characterized by inflammation, demyelination, and significant disability.[1,2] In its early stages, MS often presents as Relapsing-Remitting MS (RRMS), where patients experience alternating periods of relapses and remission. However, as the disease progresses, many patients transition into Secondary Progressive MS (SPMS), marked by continuous and unrelenting neurological decline without distinct periods of remission.[3] In addition, approximately 10–20% of patients develop primary progressive MS (PPMS) characterized by a steady and gradual deterioration of function from the onset.[3]

The spatial and temporal variability is a defining feature of the disease, as lesions occur unpredictably in different areas of the CNS at various times.[4,5] This emphasizes the complexity of disability in MS which stems from the coexistence of impairments across multiple domains, including motor and non-motor dysfunction (i.e., fatigue and pain) and cognitive functions.[6–8] These overlapping disturbances interact in a way that compounds the overall burden of the disease, making individualized care essential.

Over the past three decades, substantial progress has been made in understanding and treating RRMS.[3] However, the management of SPMS and PPMS remains limited, often focusing solely on symptom management.[9] This underscores the need for specific approaches in the management of particularly patients with PPMS and SPMS. Given the intricate interplay of symptoms across multidimensional domains, it becomes crucial to implement treatment strategies that address this complexity. A multimodal approach would be essential to create synergistic effects, but it must also be grounded in the pathophysiology of the disturbances and the neurobiological mechanisms underlying functional recovery in MS.[10,11] Given the increased financial implications associated with instances of relapse and an exacerbation of symptoms, the implementation of measures aimed at decelerating the progression of the disease may also prove instrumental in reducing the economic burden of MS.[12]

Rehabilitation plays a crucial role in the management of MS,[11,13] particularly when the disability level prevents patients from living independently and increases caregiver burden. However, in the absence of sufficient knowledge about the disease pathophysiology, the development of effective rehabilitation interventions becomes challenging. This is particularly evident in PPMS and SPMS, where rehabilitation often relies on multidisciplinary care models typically used for RRMS, without taking into account specific clinical challenges such as the scarcity of research dedicated to the progressive forms, the difficulty in providing long-term, expert-supervised rehabilitation without overwhelming healthcare costs, and the need for continuous monitoring of symptoms in an unsupervised environment.[6,8]

In this context, digital telerehabilitation offers a promising solution.[8,14–18] Utilizing advanced information and communication technologies allows for the remote delivery of rehabilitation either synchronously or asynchronously and unsupervised monitoring.[8,19] This approach might enhance the functional recovery process by incorporating engaging therapies such as exergames, virtual reality, and augmented reality feedback,[14,16–18,20] acting on empowerment and self-management.[21,22] Evidence suggests that neuroplasticity changes spreading across functional systems reflecting maladaptation contribute to sustaining disability.[23,24] For instance, maladaptive plasticity occurs within the CNS because of learned upper limb disuse[23–25] and could explain the functional decline among clinical stages and forms of MS.[24] The distinct contribution of this study lies in its exclusive focus on PPMS and SPMS, augmenting conventional in-hospital rehabilitation with home-based technological interventions informed by core principles of motor learning and adaptive plasticity.[11,26,27] By addressing this under-researched population, the study aims to provide robust evidence on the clinical efficacy of these interventions, while also generating critical data on their economic sustainability. This will not only advance scientific knowledge in the field but also offer valuable insights for policymakers regarding the cost-effectiveness and long-term feasibility of such integrated management approaches.

Objectives

The primary aim of this study is to evaluate the effectiveness of in-hospital rehabilitation followed by a home-based Digital Telerehabilitation program on mobility against in-hospital rehabilitation alone in patients with PPMS and SPMS.

Secondary aims include evaluating the intervention's impact on clinical, physiological, psychological, and economic outcomes. The patients' perspectives and experiences with Digital Telerehabilitation using quantitative and qualitative methods will be evaluated.

Methods

The study's protocol was developed in accordance with the "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) guidelines (Table 1).[28] The study will be conducted in compliance with the latest revisions of the Declaration of Helsinki and the Oviedo Declaration to ensure adherence to the principles and procedures of good clinical practice and to local legislation (Italian law).

Table 1. SPIRIT diagram for the schedule of enrollment and interventions in this parallel arm study design.

	Study period			
	Baseline	Post-allocation		
Timepoint	*T0*	*T1*	*T2*	*T3*
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Recruitment	X			
Allocation	X			
INTERVENTIONS:				
Conventional therapy	⟷			
Digital Telerehabilitation		⟷	⟷	
Self-management		⟷	⟷	
ASSESSMENTS:				
Demographic characteristics				
Age	X			
Education	X			
Sex	X			
Clinical characteristics				
EDSS	X			
MMSE	X			
Medical history	X			
Concomitant medications	X			
Primary endpoint examination				
TUG	X	X	X	X
Secondary endpoint examination				
MSFC	X	X	X	X
EEG during MSFC	X	X	X	X
EMG during NHPT	X	X	X	X

(continued)

Table 1. Continued.

	Study period			
	Baseline	Post-allocation		
Timepoint	*T0*	*T1*	*T2*	*T3*
Kinematics during NHPT	X	X	X	X
FSS	X	X	X	X
ABC	X	X	X	X
MAM-36	X	X	X	X
Number of falls in the previous month	X	X	X	X
TUG - Cognitive	X	X	X	X
EEG analysis during TUG - Cognitive	X	X	X	X
TUG - Manual	X	X	X	X
EEG analysis during TUG - Manual	X	X	X	X
Gait analysis	X	X	X	X
Balance assessment	X	X	X	X
BPI	X	X	X	X
HADS-A	X	X	X	X
HADS-D	X	X	X	X
Modified Ashworth Scale	X	X	X	X
Modified Tardieu Scale	X	X	X	X
MSQOL-54	X	X	X	X
EQ-5D	X	X	X	X
Volume of health services	X		X	X
MS-HRS	X		X	X
IT-iPCQ	X		X	X
CGI	X	X	X	X
EEG	X	X	X	X
B-IPQ	X	X	X	X
MPFI	X	X	X	X

(continued)

Table 1. Continued.

Timepoint	Study period: Baseline T0	Post-allocation T1	T2	T3
SEMS	X	X	X	X
Tele-healthcare Satisfaction Questionnaire–Wearable Technology			X	
In-home Digital Telerehabilitation Training Experience questionnaire			X	
Home-based monitoring		◆———◆	◆	
Risk of fall assessment		◆———◆	◆	
Adverse events			X	
Recruitment rate			X	
Number of dropouts			X	

T0 = before the in-hospital rehabilitation program; T1 = after the in-hospital rehabilitation program; T2 = 12 weeks after discharge; T3 = 24 weeks after discharge; EDSS = Expanded Disability Status Scale; MMSE = Mini Mental State Examination; TUG = Timed Up and Go Test; MSFC = Multiple Sclerosis Functional Composite; EEG = Electroencephalography; EMG = Electromyography; NHPT = Nine Hole Peg Test; FSS = Fatigue Severity Scale; ABC = Activities-specific Balance Confidence; MAM-36 = Manual Ability Measure-36; BPI = Brief Pain Inventory; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression; MSQOL-54 = Multiple Sclerosis Quality of Life-54; EQ-5D = EuroQol five-dimensions; MS-HRS = Multiple Sclerosis Health Resource Utilization Survey; IT-iPCQ = iMTA Productivity Cost Questionnaire; CGI = Clinical Global Impression; B-IPQ = Brief Illness Perception Questionnaire; MPFI = Multidimensional Psychological Flexibility Inventory; SEMS = Self-Efficacy for Multiple Sclerosis Scale.

Table 2. Inclusion and exclusion criteria.

Inclusion Criteria
• Age 18–75. • Diagnosis of PPSM or SPMS.[31] • Mild to moderate balance impairments with increased fall risk, defined as TUG > 8.4 s.[32] • Kurtzke Expanded Disability Status Scale (EDSS) lower than 7. • Acceptable level of digital skills. • The presence of the caregiver.
Exclusion criteria
• Other conditions that may affect motor function. • Mini-Mental Status Examination <24/30. • Severe visual deficits (daltonism and visual acuity deficit). • Unable or refusal to attend the rehabilitation treatment. • Lack of technological skills • Absence of technological tools

Trial design

This multicenter, single-blind randomized controlled trial (RCT) with 2-parallel arms will compare outcomes between the experimental group (EG) and control group (CG). The project will involve two Neurorehabilitation Units - Verona University Hospital and Ferrara University Hospital. After the screening, an external administrator will generate a block randomization list at each unit using an automated randomization system (www.randomization.com) with a 1:1 allocation ratio. Participants' disability will be assessed using the Expanded Disability Status Scale (EDSS), which rates disability from 0 (normal function) to 10 (death from MS) across various functional systems, including motor, sensory, visual, and cognitive domains. Individual system scores will be reported to highlight the most impaired areas. Trained neurologists will conduct baseline assessments following the standard EDSS protocol.

Patients will be stratified based on EDSS cut-off score of six. Group allocation will be kept concealed through a computer-based algorithm created by an independent statistician.

All patients will receive an individualized in-hospital rehabilitation program consisting of ten sessions (1 hour/day, 3 days/week) delivered by a qualified physiotherapist in neurorehabilitation at each participating unit. Following this, the EG will engage in a 12-week individualized

Table 3. In-clinic sensory integration balance training program.

Self-destabilization exercises		
Medio-lateral weight transfer	In stance with feet placed shoulder-width apart, transfer the body weight medio-laterally from the right to the left foot.	Improve correct use of ankle and hip strategy during static condition; improve quick change of strategy from ankle to hip and vice versa.
Postural transfers	Sitting in a chair without armrests, with feet placed shoulder-width apart on the floor, sit-to-stand while grasping a glass of water.	Improve correct use of ankle and hip strategy during postural transfers; improve coordination between upper and lower limbs (dual motor tasking)
External Destabilization Exercises		
Unstable surfaces	In stance work on progressively thicker compliant surfaces (1.5, 3.5, and 8 cm) according to patient's abilities.	Improve correct use of ankle, hip, and stepping strategy during static condition; improve quick change of strategy; improve ability to orientate the trunk in space.
Swiss ball	Maintain balance while sitting on a Swiss ball, with feet placed shoulder-width apart; in the second part of the exercise, the patient alternatively raises the right and the left leg from the floor.	Improve trunk control, orientation, and stability.
Self-destabilization and external destabilization exercises		
Dual-task	Keep walking while quickly changing direction (forward, backward, sideways). Keep walking while bouncing a ball and switching from right to left hand.	Improve correct use of all strategies during dynamic conditions; improve quick change of strategy. Improve correct use of all strategies during dynamic conditions; improve quick change of strategy; improve proper reaction to unexpected postural destabilization in all directions.
Biofeedback technology		
Stand hip abduction (exergame)	In a standing position, perform hip abduction reach the targets projected on the screen, and follow the feedback	Improve correct use of ankle and hip strategy during static condition; improve quick change of strategy from ankle to hip and vice versa. Improve trunk control, orientation, and stability.
Squat (exergame)	In a standing position, perform a squat reach the targets projected on the screen, and follow the feedback	Improve correct use of ankle and hip strategy during dynamic conditions.
Bipodalic balance – eyes open	Maintain balance while standing on a static balance board following visual feedback.	Improve correct use of ankle and hip strategy during static condition; improve quick change of strategy; improve ability to orientate the trunk in space.
Dynamic weight bearing frontal and side lounge on static balance board (exergame)	Perform a frontal/side lounge, reach the targets projected on the screen, and follow the feedback	Improve correct use of all strategies during dynamic condition; improve quick change of strategy from hip to stepping and vice versa.

Digital Telerehabilitation program (1 hour/day, 3 days/week) while the CG will not receive any additional therapy beyond general self-management instructions. Patients could not participate in other rehabilitation interventions during the study. No other restrictions on physical activity outside of the study protocol will be impose.

Sample size

To date, the effects of a Digital Telerehabilitation program on this population have not been studied. Nonetheless, we estimated a medium effect size ($d = 0.63$) for the primary outcome, the Timed Up and Go (TUG) Test between the EG and the CG drawing from the findings of Straudi et al. (2022).[29] With these assumptions, 70 patients (35 per group) are necessary to achieve a 80% power and an alpha (probability of type 1 error) of 5%. Assuming a 10% of drop-out, 78 patients (39 per group) are necessary to perform the study.[30]

Study population

Consecutive outpatients with PPMS and SPMS, referring to the participating units (Verona and Ferrara University Hosptitals) will be screened for eligibility. Informed consent will be obtained in writing from all participants after they have been fully briefed on the experimental nature of the study. The study will be conducted following the Declaration of Helsinki, approved by the Local Ethics Committee, and registered with ClinicalTrials.gov (NCT06485115).

Inclusion and exclusion criteria. The inclusion and exclusion criteria are reported in Table 2. A custom questionnaire will be used to assess participants' familiarity with technology, comfort with digital tools, and perceived ease of use. The EG will be trained in the use of digital devices during the final two sessions of in-hospital rehabilitation. This will enable researchers to confirm patients' confidence in the devices and address any issues through direct discussions.

A subgroup of patients meeting specific inclusion criteria will undergo electroencephalography (EEG) evaluation. These criteria include the absence of metallic implants in the brain, no history of brain surgery, no use of medications that alter cortical excitability or potentially affect brain plasticity, and right-handed dominance. Patients who do not meet the criteria for EEG assessment will still be eligible to participate in the overall study.

Dropout criteria. The patients who do not attend all sessions and/or fail to complete all clinical and instrumental assessments will be classified as dropouts. However, data analysis will include all selected and randomized patients, following the "Intention-To-Treat" analysis.

Trial interventions

In-Hospital rehabilitation sessions. All patients will participate in ten in-hospital rehabilitation sessions (1 hour/day, 3 days/week) over a period of approximately 3 weeks. The rehabilitation will consist of exercises aimed at restoring normal movement patterns within a multidisciplinary etiological framework. Treatment will be individualized according to each patient's needs, adhering to general physiotherapy principles for MS.[33,34] The content of each session will incorporate balance exercise using task-oriented approaches, along with biofeedback technology (Euleria Lab, Rovereto (TN) -Italy). The goal is to enhance functional movement, balance and postural control. Each session will begin with a brief warm-up consisting of upper and lower limb stretching exercises, combined with gentle self-applied joint mobilization while standing. This will be followed by a series of 10 specific exercises designed to target balance and motor control. The exercises will include: 2 self-destabilization, 2 external destabilization, 2 combined self-destabilization and external destabilization exercises, and 4 with biofeedback technology (Table 3). Each exercise will be repeated 2 to 5 times over a duration of 5 minutes, depending on the patient's capacity. The difficulty will progressively increase based on the number of repetitions, tasks complexity (e.g., increasing stepping distance or using a more compliant surface), and the duration of maintaining positions. For consistency across all sites, the same physical therapist will oversee both the experimental and control groups during the in-hospital phase at each unit.

Experimental group training. Patients in the EG will receive additional training in the final two in-hospital sessions, focused on using the Digital Telerehabilitation device for home-based training (Euleria Home, Rovereto, TN, Italy). This training will ensure the patient's technology susceptibility in the home-based digital telerehabilitation.

After completing the in-hospital rehabilitation sessions, patients in the EG will continue with the home-based digital telerehabilitation for a total of 36 sessions (50 minutes/day, 3 days/week, 12 weeks). This program incorporates asynchronous sessions allowing patients to complete their exercises independently at home. If necessary, a caregiver can supervise these sessions to ensure safety and adherence.

The Digital Telerehabilitation system (Euleria Home, Euleria Health) utilizes a wearable sensor and an app on a tablet. This setup guides patients through a customized exercise program designed by a healthcare professional. The sensor, worn on different body segments, tracks movements and provides real-time feedback on balance, joint angles, and exercise repetitions. To begin a session, patients wear the sensor, launch the app, and follow the exercise

Table 4. Home-based Digital Telerehabilitation program

Type of exercise	Task explanation	Expected impact
Trunk and Upper Limb Exercises		
Upper limbs forward flexion	In the standing position, flex forward upper limbs, keeping the elbows extended.	Improving upper limbs ROM, shoulder, and elbow strategy.
Upper limbs abduction	In a standing position, abduct the upper limbs while keeping the elbows extended.	Improving upper limbs ROM, shoulder, and elbow strategy.
Trunk forward flexion	In a standing position, flex your trunk while keeping your knees extended	Improving trunk ROM and stretching the posterior kinetic chain.
Lower Limbs Exercises		
Hip flexion	In the standing position, flex the hip alternatively	Improving lower limbs ROM and strength. Improve correct use of ankle, hip, and trunk strategy during dynamic conditions.
Hip extension	In the standing position, extend the hip alternatively	Improving lower limbs ROM and strength. Improve correct use of ankle, hip, and trunk strategy during dynamic conditions.
Hip abduction	In the standing position, abduct the hip alternatively	Improving lower limbs ROM and strength. Improve correct use of ankle, hip, and trunk strategy during dynamic conditions.
Side lunge	In a standing position, perform a lateral lunge.	Improve correct use of all strategies during dynamic conditions; improve quick change of strategy from hip to stepping and vice versa.
Semi-squat	In a standing position, flex hip and knee to perform a semi-squat	Improve correct use of ankle, hip, and trunk strategy during dynamic conditions.
Weight transfer in semi-forward lounge	In a standing position, place the foot on the forward step, and flex the hip and the knee to perform a semi-forward lounge.	Improve correct use of all strategies during dynamic conditions; improve quick change of strategy from hip to stepping and vice versa.
Balance Exercises		
Lateral transfer of body weight	Shift the body weight toward the right and left direction.	Improve the correct use of ankle and hip strategy during dynamic conditions.
Change of direction simulation	Starting from the static position supported by both feet, the whole body is turned to the right and then to the left direction by taking small steps.	Improve the correct use of all strategies during dynamic conditions. Improve the quick change of strategy from hip to stepping and vice versa. Improve the coordination.
Balance in tandem position	Maintain balance while standing on a reduced firm surface with feet in tandem position.	Improve the correct use of ankle and hip strategy during static conditions with a reduced support base. Improve the quick change of strategy from ankle to hip and vice versa.
Walk in place with dual-task	Keep walking in place while switching a ball from the the right to the left hand.	Improve correct use of all strategies during dynamic conditions; improve quick change of strategy; improve proper reaction to unexpected postural destabilization in all directions.
Monopodalic proprioception	In the monopodalic position, perform the swing phase of the step with the other leg.	Improve the correct use of all strategies during dynamic conditions. Improve the quick change of strategy from hip to stepping and vice versa. Improve the coordination.

instructions on the tablet, utilizing biofeedback to guide their movements.

A physiotherapist at each unit will design the individualized training plan for these sessions. Preselected exercises, chosen from an extensive library, will focus on balance and motor activities for both the upper and lower limbs, primarily performed in a standing position. The physiotherapist will configure the exercise plan during the first session, taking into account the patient's clinical assessment, preferences, and functional level. Subsequent sessions will employ a random practice approach within the Digital Exercise Therapy framework, with the progression of exercises tailored to the patient's abilities and progress. Each session will begin with a brief warm-up that includes gentle stretching of the upper and lower extremities, combined with self-applied joint mobilization. The core of the session will feature 14 specific exercises, selected by the physiotherapist based on the patient's clinical condition and ongoing improvements (Table 4). These exercises will primarily target balance and range of motion for both upper and lower limbs, with most activities performed in a standing position. If necessary, a caregiver will be present during the sessions to ensure the patient's safety and provide assistance.

Ongoing monitoring and adjustments. The physiotherapist will remotely track patient performance through a cloud-based management system, which allows for the ongoing personalization of the exercise program. The system provides various types of feedback, including visual and augmented feedback, such as knowledge of results and performance. This data enables the physiotherapist to assess key metrics like adherence (number of sessions completed), session duration, and movement performance (e.g., range of motion).

Synchronous sessions. Synchronous sessions will be held every 3–4 week, or as needed, to address any challenges, provide solutions, and make necessary adjustments to the rehabilitation plan based on patient feedback and performance data. During these sessions, the physiotherapist can interact directly with the patient, either via video call or chat within the digital telerehabilitation platform, ensuring continuous support and oversight.

Control group training. Patients in the CG will be advised to continue performing the self-management activities they learned during the in-hospital rehabilitation sessions but without home-based digital telerehabilitation devices or supervision, as part of the usual care protocol.[35,36]

Outcome measures

Data collection. Socio-demographic data, including age, gender, education level, and employment status, along with clinical history, will be collected by a medical doctor at enrollment. In each unit, a physician blinded to group assignment will gather primary and secondary clinical outcomes at four-time points according to the SPIRIT diagram: before the intervention (T0), after the in-hospital rehabilitation program (T1), at 12 weeks (T2), and at 24 weeks (T3) follow-up. Feasibility measures including recruitment rates, intervention acceptability (based on dropout numbers), and safety (tracking any adverse events such as falls or near falls reported in the patient's log) and the patient perspectives and experiences with Digital Telerehabilitation will be gathered at T2. Data on healthcare service usage, as well as direct and indirect costs, will be collected at T0, T2, and T3. During the in-hospital rehabilitation sessions, activities will be closely monitored using sensors designed to estimate the risk of falling. This is critical for tailoring effective home-based rehabilitation programs. A specialized inertial sensor will be placed on the patient's forehead using an elastic band to detect near falls during balance exercises.

Primary outcome measure. The primary outcome will be the change in patient mobility measured by the TUG from T0 to T2 (Euleria Lab, Rovereto – TN, Italy).[32]

Secondary outcome measures

Clinical Outcomes. Secondary outcome measures will assess changes from T0 to T2 of the following.

Functional and motor-cognitive interaction measures

The Multiple Sclerosis Functional Composite (MSFC) evaluates gait, upper extremity function, and cognition.[37] Motor-cognitive interaction will be investigated by the dual-task TUG test in the cognitive and manual versions.[38] The total time required for these assessments is approximately 60 minutes.

To enhance the information obtained from the MSFC and the TUG, we will instrument the assessment with EEG, electromyography (EMG), and kinematic analysis to gain deeper insights into the physiological processes underlying task performance. During the administration of these assessments, the participant's brain activity will be recorded using EEG. Data will be recorded using an 8-channel wearable and wireless system (Mindtooth touch headset) provided with gel-free sensors and a click-ok amplifier integrated with the headset to allow EEG recording during functional activities such as walking, reaching, and grasping. The system is designed so that the eight electrodes are placed at AFz, AF3, AF4, AF7, AF8, Pz, P3, and P4, and the ground and reference electrodes are placed on the two mastoid processes. Its lean design and the gel-free electrodes allow a simple but accurate set-up, taking around 5–10 minutes maximum.

In assessing the mental workload, the system has shown high reliability in laboratory and realistic settings, performing not significantly different from the gold standard based on gel electrodes.[39] By capturing brain activity during tasks, EEG data will provide insights into cognitive engagement, attention, and mental effort during the MSFC.

The muscular activity and upper limb kinematics will be recorded during the Nine Hole Peg Test (NHPT), a component of the MSFC. Surface electromyography (sEMG) will be used to capture muscle activation patterns, offering a noninvasive detailed look at neuromuscular activation during the task and how they contribute to fine motor control. Meanwhile, an Inertial Measurement Unit (IMU) will be used to record the kinematics of the upper limb, quantifying movement characteristics such as speed, acceleration, and joint angles during the test. By combining sEMG and IMU data, we can better understand the dynamics of muscle activation and movement, which will help in assessing motor performance and detecting subtle impairments. The instrumentation of the MSFC and TUG evaluations will not extend the overall assessment time, except for the additional setup of the technology, which takes approximately 15 minutes. All evaluations will be conducted on the same day, beginning with the functional and cognitive outcomes, followed by the psychological assessments. Patients participating in the EEG protocols will be evaluated on a separate day to ensure adequate time for these procedures.

The number of falls reported by patients in the previous month, muscle tone changes will be measured using the Modified Ashworth Scale and the Tardieu Scale.[40,41]

Gait and balance will be evaluated in the hospital using advanced technology from Euleria Lab (Rovereto, TN, Italy). Balance will be assessed in both single and dual-task conditions under three scenarios: eyes open, eyes closed, and dome condition. Measurements will include the length of the center of pressure (CoP) trajectory (mm) and sway area (mm^2). Gait performance will be measured in single and dual-task conditions (motor, cognitive, and visual-fixation) by assessing gait speed (cm/s), cadence (steps per minute), and stride length (cm), while automaticity will be evaluated using variability measures.

Patients reported outcome measures. Patient-reported outcomes will be the "Hospital Anxiety and Depression Scale" (HADS),[42] a brief self-report questionnaire composed of 14 items describing on a 4-point scale from 0 to 3 the levels of anxiety a person is experiencing, the Fatigue Severity Scale (FSS),[43] the Activities-specific balance confidence (ABC),[44] the Manual Ability Measure-36 (MAM-36),[45] and Brief Pain Inventory (BPI) divided into intensity (range: 0–40; higher = worse) and interference (range: 0–70; higher = worse).[46] Health-related Quality of life and Self-rated perception of change outcomes will be assessed with the Multiple Sclerosis Quality of Life-54 (MSQOL-54)[47], 7-point Clinical Global Impression (CGI) with scores from 1 (very much improved) to 7 (very much worse)[48] and a generic preference-based measures, EuroQol five domains (EQ-5D) for cost-effectiveness analysis.[49]

Psychological and emotional outcomes. Quantitative and qualitative information about the intervention, from the perspectives of both patients and their caregivers, will be collected using several tools. The Brief Illness Perception Questionnaire (B-IPQ), an 8-item instrument, will assess cognitive and emotional representations of illness[50]; The Multidimensional Psychological Flexibility Inventory (MPFI), a 60-item scale, will measure the six dimensions of psychological flexibility and the six dimensions of inflexibility as outlined in the Hexaflex model[51]; The Self-Efficacy for Multiple Sclerosis Scale (SEMS) will evaluate self-efficacy in managing MS. It consists of 15 items, all starting with the statement "I am confident that I can…," rated on a 5-point Likert scale from 0 (not at all confident) to 4 (very confident). The SEMS provides two sub-scores: "Goal Setting" (items 2, 3, 4, 5, 6, 7, 8, 13, 14) and "Symptom Management."[52]

The Tele-healthcare Satisfaction Questionnaire—Wearable Technology will assess satisfaction with the wearable technology, covering six areas: benefit, usability, self-concept, privacy, loss of control, quality of life, and wearing comfort. Each area contains five statements rated on a 5-point Likert scale, from 0 (strongly disagree) to 4 (strongly agree).[53,54] Additionally, the research group will use a custom questionnaire to evaluate the patients' experiences with in-home Digital Telerehabilitation, referred to as the "EG Treatment Experience" questionnaire. The questionnaires will be completed via an online form, under the supervision of personnel, to streamline the process and minimize patient burden.

Physiological outcomes. In addition to the physiological measures collected during the instrumentation of the MSFC and TUG tests, further assessments will focus on brain activity networks during upper limb tasks and mobility measures in an unsupervised environment. Only patients eligible for EEG will undergo evaluations at T0 and T2, during which physiological indices will be collected while performing motor observation, execution, and motor imagery tasks (using EasyCap + ActiCHamp plus, Brain Products GmbH; E-Prime-2, Psychology Software Tools, Pittsburgh, PA).[55] Furthermore, home-based monitoring will be conducted at T1, where each patient will be equipped with two wearable sensors (Axivity AX6) 6-axis logging accelerometers placed on the lower back and a lower limb. These sensors will monitor motor activity, sleep, and energy expenditure for five consecutive days in an unsupervised environment. The data collected will be periodically transmitted to the research center for analysis, and patients will also keep clinical diaries to document their subjective evaluations of motor activity, with a particular focus on gait and general activity levels. These assessments will enable us to gather valuable insights into potential brain plasticity network changes induced by the intervention, as well as the generalization of these effects in an ecological, real-world environment. By combining EEG-based brain activity measurements during upper limb tasks with home-based mobility monitoring, we can assess both the neurological and functional impacts of the study, providing a comprehensive view of the intervention's efficacy. The EEG assessment, estimated to take approximately 90 minutes, will be conducted on a subgroup of patients based on their availability. In contrast, the setup and application of the wearable sensors will require only 15 minutes, with no additional time demands on the patients as they will wear the sensors during their daily activities.

Economic outcomes. An economic evaluation of the introduction of the Digital Telemedicine program will be carried out alongside the clinical trial.[56] The type of economic analysis chosen refer to the health technology assessment (HTA) framework.[57] According to Drummond economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences,"[58] and has the goal to provide robust information for informed choices and allocate resources for the greatest possible utility for the health systems and society. The main types of economic analysis in healthcare are cost minimization analysis, cost-efficacy analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). The present study will employ a cost-utility analysis (CUA) approach as its primary methodology. Cost-Utility Analysis (CUA) incorporates health outcomes in terms of quality-adjusted life years (QALYs), measured using the EQ-5D questionnaire. The results are expressed as the cost per QALY gained by the new technology compared to its alternatives. To assess cost-effectiveness, the incremental cost-effectiveness ratio (ICER) will be applied.[59] The potential for variability in cost categories and effectiveness parameters, as well as the possibility of technological infrastructure limitations for specific patient groups, will be addressed through sensitivity and subgroup analyses.[60] These analyses will also examine setbacks due to the platforms or socioeconomic disparities (age, gender, education level, working status) that might affect patient groups' ability to use telemedicine infrastructure and, therefore, impact cost.

The Digital Telemedicine program's economic impact will be assessed by measuring different types of costs.

The costs used for the cost-effectiveness analysis will be the program costs (time of health professionals, materials used, etc.), the direct healthcare costs (as healthcare service uses, costs of outpatient health services, hospitalization, and purchase of medications), direct non-healthcare costs (the costs of transportation and caregiving or informal care), indirect costs (as productivity loss due to treatments or disease setbacks). Regarding the implementation and management activities fixed and variable costs will be identified to understand the volume of patients involved to reach economic convenience for the fully operational Digital Telemedicine program.

Direct healthcare costs will be assessed using the Multiple Sclerosis Health Resource Utilization Survey (MS-HRS)[61] adapted for the Italian context. The MS-HRS is a validated instrument for the resource use by MS patients. The volumes of health services will be collected at baseline, encompassing the resources used 6 months before the start of the study and at T3 estimating the resource use during the entire trial duration.

To lower recall bias and missing values, patients will receive a resource use log (RUL).[62] A RUL is, in essence, a diary that is given to patients at baseline for them to prospectively record resources used. Unlike a diary, data in the RUL are neither collected nor used for analysis. It is designed as a memory aid to assist patients in completing a RUQ at follow-up.

The direct nonhealthcare cost collection will be based on the social part of the iMTA Medical Consumption Questionnaire.[63]

Indirect costs will be measured using a validated log as the TheiTA Productivity Cost Questionnaire for productivity loss.[64] This questionnaire is validated over a shorter time period and will be administered at T0, T2, and T3.

Statistical analysis

The primary analysis will be based on intention-to-treat methods. Missing data will be handled using last observation carried forward techniques. The descriptive statistic will include mean, standard deviation, and Confidence Interval (or median and Quartiles) calculation. The parametric or nonparametric test will be applied according to the data distribution evaluated by Shapiro–Wilk and Kolmogorov–Smirnov. The parametric test will include Repeated Measure Analysis of Variance (ANOVA) with "Group" (EG and CG) as between factor, "Time" (T0, T1, T2, and T3) as within factor, and "Time×Group" interaction. The nonparametric test will be the Friedman test. The main effect is significant with $P < .05$. Post hoc comparisons will be performed using paired and unpaired T-tests (Mann–Whitney or Wilcoxon test) and corrected using Bonferroni correction. Statistical analysis will be performed using the SPSS statistical software (IBM SPSS Statistics for Mac, ver.26, Armonk, NY, USA). The patients' perspectives will be analyzed using descriptive statistics for quantitative data and inductive content analysis for qualitative data.

An economic evaluation of the introduction of the new technology will be carried out. In detail, cost and health outcomes will be synthesized in a cost-effectiveness model highlighting the Digital Telemedicine program's value for money (or not) vs. usual care. For the economic modeling, an analytical decision model (such as a Decision tree or Markov model) method will be used to analyze the cost-effectiveness (CE) of the telerehabilitation program. The choice of the model will depend on the ability to represent all the possible disease paths. In addition, the analysis will be carried out to account for the parameter uncertainty together with scenarios analysis and what-if analysis (TreeAge Pro 2022 R2).

Results

The data collection phase will start in September 2024. The project is scheduled to conclude within two years, with results expected to be finalized by 2026.

The results of this project could be relevant for advancing dedicated rehabilitation pathways for PPMS and SPMS patients through Digital Telerehabilitation. For the first time, we will compare the effects of a hybrid model comprising an in-hospital rehabilitation program followed by a home-based Digital Telerehabilitation intervention (experimental intervention) versus an in-hospital rehabilitation program without any additional therapy (conventional intervention) by a full-powered RCT on a selected sample of patients with PPMS and SPMS. The home-based Digital Telerehabilitation could provide motor and cognitive training within an engaging environment supporting the patient's empowerment and self-management under the supervision of expert clinicians. Moreover, the evaluation of the neurobiological correlation through the EEG could provide implications to support clinical guidelines on managing patients toward a more sustainable MS rehabilitation. Finally, the health economic analysis will establish the resources required to offer the new program, estimate intervention costs, and the cost-effectiveness.

Discussion

Despite significant progress over the past three decades in understanding and treating RRMS, therapeutic options for the progressive MS remain limited, representing a critical unmet need. Indeed, while recently, Telerehabilitation has shown promise in increasing adherence to exercise-based physical therapy,[65] empowering patients in their care management,[14,16–18,65,66] and enhancing efficiency,[21,22] up to date, there is a striking absence of studies with larger sample sizes, including people with SPMS or PPMS, evaluating the long-term outcomes, assessing of the effects on quality of life and reporting healthcare cost-effectiveness analysis data.[6] A significant study on Telerehabilitation for individuals with MS has provided key insights into the factors that affect the adoption and completion of physical therapy treatments during the early phases of the COVID-19 pandemic. These insights cover both patient-related factors, such as the level of disability and employment status, as well as therapist considerations for creating safer, more effective, and accessible hybrid models of care. By combining in-person visits with Telerehabilitation, hybrid care models may improve access, attendance, and the completion of physical therapy for patients with demyelinating diseases.[16] In alignment with these findings, our study incorporates a Digital Telerehabilitation program as part of a multidisciplinary rehabilitation plan, rather than comparing the two approaches in isolation.

The rationale for conducting a RCT on the effectiveness of Digital Telerehabilitation is compelling. As an emerging field of research, Digital Telerehabilitation has been increasingly recognized as a potentially effective alternative to traditional rehabilitation methods for individuals with neurological disabilities.[14,65,67–69] A tailored digital program integrated in the multidisciplinary care not only promises usability but also provides a more personalized and engaging rehabilitation experience for patients. Accordingly, we expect that tailored digital programs will be both usable and beneficial, offering patients a more personalized and engaging rehabilitation experience.

For people with MS, particularly those with progressive forms, accessibility to care remains a persistent challenge. Geographical distance, the scarcity of trained professionals, and various time and financial constraints are often major barriers. Digital Telerehabilitation offers a solution by allowing remote access to essential services, ensuring that patients can receive high-quality multidisciplinary care regardless of location. This is especially relevant for individuals living in rural or underserved areas, where access to care is often limited.[16,70–73] We expect that our approach could offer remote access to these crucial services, ensuring that patients continue to receive high-quality care from multidisciplinary experts, regardless of where they live.

In addition to improving access, Digital Telerehabilitation could have economic benefits. Although some studies suggest that Telerehabilitation can reduce healthcare costs,[21,22] it remains crucial to confirm these findings specifically in patients with progressive MS. While the initial investment in technology may seem high, the long-term potential to improve patient outcomes while reducing overall healthcare expenditures is significant. By decreasing the need for frequent in-person visits, Digital Telerehabilitation could also help patients and their families cut down on travel expenses and time commitments, contributing to a more efficient model of care. We expect that by reducing the need for frequent in-person visits to healthcare facilities, Digital Telerehabilitation could help to cut down on travel expenses and time commitments for patients and their families, making care more efficient.

Moreover, Digital Telerehabilitation offers flexibility, allowing patients to incorporate rehabilitation seamlessly into their daily routines. This adaptability provides patients with the freedom to receive care at times and locations that suit them best. Advanced technology can enhance this experience, making therapy more interactive and engaging while fostering stronger connections between the brain and motor functions.[16,74–76] Indeed, enhanced feedback mechanisms play a crucial role in motor and cognitive rehabilitation.[77] We expect that this adaptability, combined with an interactive environment, will not only boost patient engagement and adherence to prescribed programs but also facilitate long-term positive outcomes.

The unique design of this experimental study offers an invaluable opportunity to provide the scientific community with robust, high-quality data. This, in turn, will enhance the evidence base needed to inform clinical management guidelines and support decision-making for policymakers in making data-driven decisions for optimizing patient care.

Strength and limitation

To our knowledge, this is the first fully powered RCT examining the effectiveness of an hybrid model combining Digital Telerehabilitation with conventional therapy in patients with progressive MS. A key strength of this study lies in its methodological rigour and the large sample size, achieved by merging data from two units with extensive experience and a robust interdisciplinary research team. We will conduct a comprehensive assessment, including clinical, monitoring, physiological, psychological, and economic measures, with a long-term follow-up. Additionally, this study will offer insights into patients' perspectives and experiences with Digital Telerehabilitation.

Our study may have some limitations. Despite the significant advantages of Telerehabilitation regarding flexibility and accessibility,[16] some patients may experience difficulties using the technological equipment. Furthermore, individuals living in rural and underserved areas might face issues with internet connectivity.

Implications. This RCT could offer implications at several levels. From a clinical perspective, our findings could enrich the pathways dedicated to progressive MS through a confirmatory study on the effectiveness and cost-effectiveness of the Digital Telerehabilitation approach.

From a research perspective, our results may fill the gap in the actual literature on progressive MS. The evaluation of neurobiological correlations through EEG could provide new insights into both adaptive and maladaptive plasticity mechanisms. Meanwhile, integrating individuals' experiences could guide future quantitative research by identifying research priorities and relevant outcomes for individuals with progressive multiple sclerosis.

Conclusions

Our results could provide first-time information on the effectiveness of a hybrid model including in-home Digital Telerehabilitation for supporting clinical guidelines on managing patients with PPMS and SPMS toward a more sustainable MS rehabilitation and provide preliminary data on cost-effectiveness to inform policymakers and the National Health System.

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Ethical Approval: The study was approved by the Local Ethics Committee and registered as a clinical trial on ClinicalTrials.gov (NCT06485115). Prospective participants will be fully informed of the project's aims and procedures. A reporting procedure will ensure that any serious adverse events are reported to the Principal Investigator. At enrollment, informed consent forms will be made available to all participants engaged in the project, and the patient's written informed consent form will be obtained before his/her participation in the study. Personal information about potential and enrolled participants will be collected, shared, and maintained to protect confidentiality before, during, and after the trial. Communication and dissemination activities will include the project's visual identity, public website, social media, videos, and press releases.

Consent to participate: Informed written consent will be obtained from all participants before the study initiation.

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