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Efficacy of telerehabilitation with digital and robotic tools for the continuity of care of people with chronic neurological disorders: The TELENEURO@REHAB protocol for a randomized controlled trial

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Abstract

Context: Chronic Neurological Disorders (CNDs) are among the leading causes of disability worldwide, and their contribution to the overall need for rehabilitation is increasing. Therefore, the identification of new digital solutions to ensure early and continuous care is mandatory.

Objective: This protocol proposes to test the usability, acceptability, safety, and efficacy of Telerehabilitation (TR) protocols with digital and robotic tools in reducing the perceived level of disability in CNDs including Parkinson's Disease (PD), Multiple Sclerosis (MS), and post-stroke patients.

Design, Setting, and Subjects: This single-blinded, multi-site, randomized, two-treatment arms controlled clinical trial will involve PD (N = 30), MS (N = 30), and post-stroke (N = 30). Each participant will be randomized (1:1) to the experimental group (20 sessions of motor telerehabilitation with digital and robotic tools) or the active control group (20 home-based motor rehabilitation sessions according to the usual care treatment). Primary and secondary outcome measures will be obtained at the baseline (T0), post-intervention (T1, 5 weeks after baseline), and at follow-up (T2, 2 months after treatment).

Main Outcome Measures: a multifaceted evaluation including quality of life, motor, and clinical/functional measures will be conducted at each time-point of assessment. The primary outcome measures will be the change in the perceived level of disability as measured by the World Health Organization Disability Assessment Schedule 2.0.

Conclusion: The implementation of TR protocols will enable a more targeted and effective response to the growing need for rehabilitation linked to CNDs, ensuring accessibility to rehabilitation services from the initial stages of the disease.

Keywords

Telerehabilitation, digital health, robotics, chronic neurological diseases, Parkinson's disease, multiple sclerosis, stroke

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Introduction

According to the Global Burden of Diseases, Injuries, and Risk Factors Study, neurological disorders are one of the major causes of disability in the world, resulting in 276 million disability-adjusted life-years.[1] In particular, Parkinson's disease (PD), Multiple Sclerosis (MS), and post-stroke are among the central chronic neurological

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disorder (CND) associated with the highest number of years of life lived with disability, resulting in limited daily activities, restrictions in social participation, and poor quality of life.[2]

Rehabilitation is relevant to the needs of people with these CNDs and consists of a multimodal, person-centred process with specific interventions targeting body structures, functions, activity/participation, and contextual factors to achieve optimal functioning.[3] To obtain functional and healthy outcomes, early, intensive, and continuous interventions are essential. Rehabilitation should start as soon as possible after the diagnosis of a neurological disorder and must be ensured for a long time after discharge.[4,5] However, policymakers and healthcare professionals seem not equipped to deal with the large need for rehabilitation. Rehabilitation services and resources for people with CNDs are limited or lacking in many developing countries, especially in low-income and developing ones.[6] Moreover, as currently provided, rehabilitation interventions are difficult to access for all those in need, especially in the initial stages of the disease.[2] Therefore, the identification of feasible and effective therapeutic solutions becomes essential to expand the offer of rehabilitation services to all those who can benefit from it, along the entire course of the disease.

The current disruptive digital and robotics technological progress represents a valuable resource to increase accessibility to rehabilitation. The use of health technologies and the provision of remote Telerehabilitation (TR) services through digital platforms represent the new frontier for integrated and long-term management of chronic neurological disability.[7,8] Previous studies in the field[9–18] investigated the feasibility and efficacy of innovative, multidimensional TR approaches. They involved new digital solutions to ensure early and continuous management of CNDs, including PD and MS, beyond the hospital walls. The principal goal was to provide patients, families, and clinicians with instruments that are clinically validated, safe, easily accessible, and usable. Moreover, robot-based treatments are developing in neurorehabilitation settings. Robot-assisted rehabilitation has proven to be effective in improving both motor[19] and cognitive[20] functions in CNDs. The use of robotic tools allows providing for more intense and controlled training within a highly personalized therapeutic plan.[21] Moreover, robotic rehabilitation tools can promote the best recovery of sensorimotor, behavioral, and motor functionalities according to the individual functional profile of each patient.[22–28] Robotic solutions are commonly adopted in clinics but also at the patient's home to assure the continuity of care for stroke patients. In fact, a further challenge the neurorehabilitation concerns the need to "*rethink the patient's home as a place of care*".[29]

In this framework, rehabilitation interventions delivered with digital and robotics solutions are ideal candidates, but just like the new drugs, these digital medical solutions will require a rigorous evidence-based approach.[8] Starting from these premises, this project will aim to evaluate the usability, acceptability, safety, and efficacy of TR protocols with digital and robotic tools in reducing the perceived level of disability in persons with CNDs using a Randomized Controlled Trial (RCT) design.

Materials and methods

The protocol of the study has been conceived as outlined in the "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) guidelines (Figure 1). The study will be conducted according to the Declaration of Helsinki, the principles of Good Clinical Practice, and in accordance with local legislation in participating countries.

Trial design and setting

This study is designed as a single-blinded, randomized, two-treatment arms controlled clinical trial involving chronic outpatients from neurorehabilitation units of IRCCS Fondazione Don Carlo Gnocchi (Milan and Rome, Italy). After the enrolment and baseline assessment, each participant will be randomized (with an allocation ratio of 1:1) to the experimental group (20 sessions of motor TR with digital and robotic tools) or the active control group (20 motor rehabilitation sessions performed at home according to the usual care treatment procedure). Randomization will be stratified according to CNDs. Primary and secondary outcome measures will be obtained at the baseline (T0), post-intervention (T1, 5 weeks after baseline), and at follow-up (T2, 8 weeks after the end of the treatment). The trial work plan is shown in Figure 2.

Sample size

According to an *a-priori* sample size calculation (using the G*Power software,[30,31]) 90 subjects (45 subjects per arm), comprehensive of up to 10% drop-off, is sufficient to detect a medium to large standardized effect size (0.695) when considering the independent comparison between two groups (two-sided unpaired *t*-test). The Effect size was obtained from our previous unpublished study that compared two groups of treatments in WHODAS 2.0[32] total score (TR group mean = -2.91 ± 8.61; UC group mean = 3.31 ± 9.26) and was chosen as a benchmark as the studies are similar in terms of methods and materials. Power calculation was conducted considering a type-I error rate of 5% ($\alpha = 0.05$) with a statistical power of 0.80.

Study population, recruitment, and randomization

According to the sample size calculation, this trial has a recruitment target of 90 CND individuals with the diagnosis of post-Stroke (N = 30), PD (N = 30), and MS (N = 30). Eligible patients who meet all inclusion criteria (see the paragraph below) will be randomized using a web-based

STUDY PERIOD			
	Baseline	Post-allocation	
TIMEPOINT	T0	T1	T2
ENROLLMENT			
Eligibility screen	X		
Informed consent	X		
Recruitment	X		
Allocation	X		
INTERVENTIONS			
Telerehabilitation	←	———	→
Usual care	←	———	→
ASSESSMENTS			
Demographic characteristics *Age* *Education* *Sex*	X		
Clinical characteristics MDS-UPDRS EDSS	X	X	X
Technological expertise *ad-hoc* questionnaire	X		
Usability and acceptability assessment SUS TAM		X	
Safety Adverse events *ad-hoc* questionnaire		X	
Primary outcome measure WHODAS 2.0	X	X	X
Secondary outcome measures MoCA TMT SDMT BDI-PC STAI-Y2 FMA-UL ARAT BBT 9-HPT mDGI Mini-BESTest ABC	X	X	X
Surrogate Markers MRI	X#	X#	X#

Figure 1. SPIRIT figure for the schedule of enrolment, interventions, and assessments in a parallel arm study design. T0 = baseline (pre-intervention phase); T1 = post-treatment assessment; T2 = follow-up assessment (8 weeks after the end of the treatment). WHODAS 2.0: WHO Disability Assessment Schedule 2.0; EDSS: Expanded Disability Status Scale; MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale; FMA-UL: Fugl-Meyer Assessment – Upper Extremity; ARAT: Action Research Arm Test; BBT: Box and Block Test; 9-HPT: Nine Hole Peg Test; mDGI: modified Dynamic Gait Index; Mini-BESTest: Mini-Balance Evaluation Systems Test; ABC: Activities Balance Confidence scale; MoCA: Montreal Cognitive Assessment test; TMT: Trail Making Test; SDMT: Symbol Digit Modalities Test; BDI-PC: Beck Depression Inventory for Primary Care; STAI-Y2: State-Trait Anxiety Inventory – Form Y2; MRI: Magnetic Resonance Imaging; SUS: System Usability Scale; TAM: Technology Acceptance Model. #Optional evaluation.

allocation concealment through a computer-based algorithm created by an independent statistician. We will adopt a stratified randomization to prevent imbalance between treatment groups. The sample will be stratified according to the clinical condition (SM, PD, post-stroke) and randomly allocated (1:1) into either the experimental

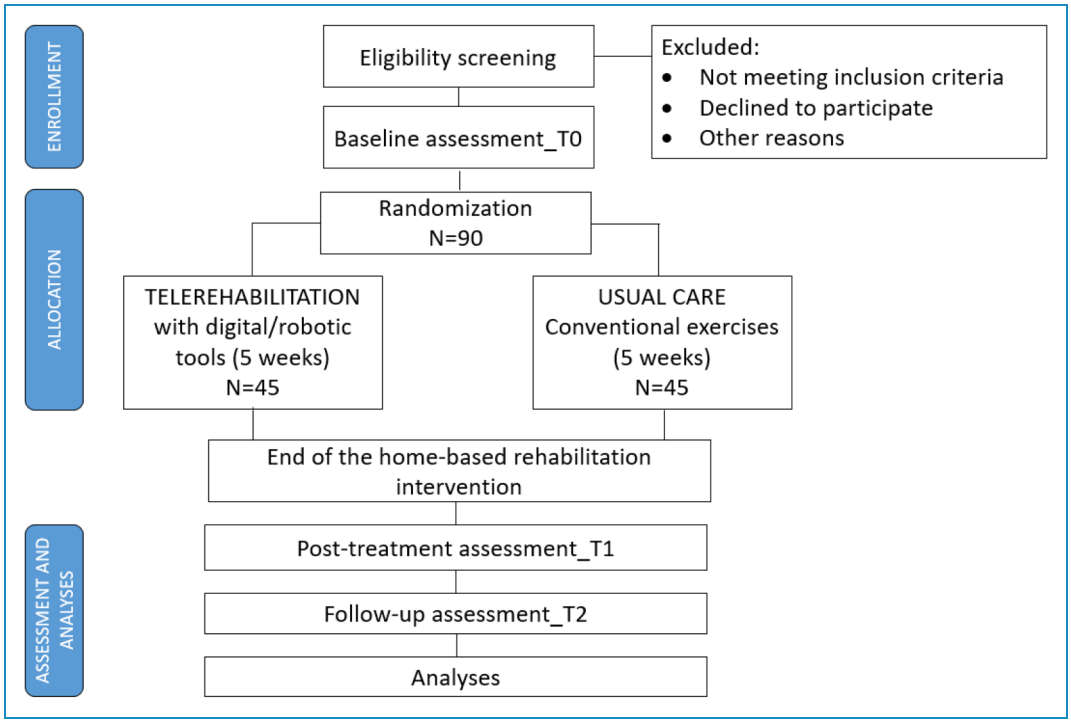

Figure 2. The trial work plan.

group or the active control group. The trial intervention will not be blinded for clinicians or patients due to its nature. Conversely, clinical endpoints and data collection from clinical/psychological questionnaires will be blinded to examiners/assessors. The statistician conducting the data analysis will be masked for the group allocation.

Inclusion and exclusion criteria

The inclusion criteria for all participants will be:

1. diagnosis of chronic post-stroke condition with ischemic or haemorrhagic stroke injury occurred 4–6 months before recruitment and with motor impairment of the upper limb >2 to the Medical Research Council scale (MRC);

   or

   diagnosis of probable PD according to MDS criteria[33] in staging between 1.5 and 3 on the Hoehn & Yahr scale[34];

   or

   diagnosis of MS, RR-SP forms, according to the criteria of MC Donald 2010[35] with disability level at the Expanded Disability Status Scale EDSS[36] < 6

2. age between 25 and 85 years;
3. preserved cognitive level at the Montreal Cognitive Assessment test (MoCA test >17.36)[37];
4. agreement to participate with the signature of the informed consent form;
5. no rehabilitation program in place at the time of enrolment;
6. stable drug treatment (last 3 months) with L-Dopa or dopamine agonists (PD group) and/or cortisone (MS group).

The exclusion criteria for all participants will be:

1. presence of comorbidities that might prevent patients from undertaking a safe home program or determining clinical instability (i.e., severe orthopedic or severe cognitive deficits);
2. presence of major psychiatric complications or personality disorders;
3. presence of severe impairment of visual and/or acoustic perception;
4. relapse ongoing/at least 3 months since the last relapse (MS group);
5. presence of "frequent" freezing as recorded at the administration of Section II (daily life activity) of the UPDRS (score ≥ 3) (PD group);
6. falls resulting in injuries or more than 2 falls in the 6 months prior to recruitment (PD and MS groups).

Trial interventions

The Trial protocol provides for the random allocation of participants to two different types of rehabilitation

treatment: Telerehabilitation treatment (TR) and Usual Care (UC), according to a single-blind, parallel arm design.

Tele-rehabilitation (TR). The TR intervention for people with PD, MS, and people post-stroke will be focused on addressing impairments and functional limitations that affect activities and participation in everyday life. For descriptive purposes, the characteristics of the TR intervention are detailed according to the FITT indices (in terms of Frequency-Intensity-Time-Type of intervention)[38]:

(a) *Frequency:* the TR group will experience 5 weeks (4 sessions/week) of TR intervention provided according to a mixed model (3 asynchronous sessions + 1 synchronous, in-clinic session/week). Participants will freely choose when to perform each home TR-session according to their preferences and needs;
(b) *Intensity:* each session will be customized according to the patient's functional abilities to ensure the progression of difficulty in rehabilitation sessions (system's feedback);
(c) *Time:* each session will last about 50 min/day;
(d) *Type:* according to the disease, patients will perform TR protocols with a digital system (TR Type A for MS and PD) or robotic tool (TR Type B for post-stroke).

TR Type A. Rehabilitation activities will be aimed at improving motor performance and balance using a task-oriented approach with Homing system technology (https://www.tecnobody.com/). The Task-oriented approach is based on well-established theories of motor learning assuming a problem-solving process focusing on tasks and activity limitation[39,40] aiming at ensuring motor practice and preserving the natural goal-directedness of movements in a functional environment.[41] The task-oriented activities will be varied to maximize transfer in daily life[42] and will be focused on improving the position and movements of the center of mass in a sitting station and/or standing in static and dynamic conditions using biofeedback techniques (see Table 1). The biofeedback signal will be based on the following components: mode, content, and timing.[43] The camera and the speaker's microphones of the Homing system will provide visual and auditory feedback on the execution of the exercises, both in terms of knowledge of performance (quality of the movement during the execution of a task) and knowledge of results (information on goal-achievement).[44] The progression of intervention will be based according to Gentile's taxonomy with static predictable tasks at the beginning and dynamic and unpredictable tasks at the end, sensory cues will be progressively changed as well. A cut-off of 70% of correct execution (defined for each exercise) will be used to switch from easy to challenging exercises.

Table 1. Examples of task-oriented activities. CoM = Centre of Mass.

Task-oriented digital activities	
Type [Description]	**Digital data flow**
Tandem [The subject stands on the floor maintaining feet in tandem]	**Measure:** CoM control in static and predictable conditions **Feedback:** VISUAL and AUDITORY
Standing on a foam [The subject is requested to maintain a standing position on a foam pillow for 30 s]	**Measure:** CoM control in static and unpredictable conditions **Feedback:** VISUAL and AUDITORY
Sit to stand [The subject is asked to perform a body transfer from sitting on a chair to a standing position]	**Measure:** CoM control in semi-dynamic and predictable conditions **Feedback:** VISUAL and AUDITORY
Step ups/step downs [The subject is asked to step-up and step-down alternating feet]	**Measure:** CoM control in dynamic and predictable conditions **Feedback:** VISUAL and AUDITORY
Move to reach [The subject is asked to reach virtual targets with forward, backward, and lateral steps]	**Measure:** CoM control in dynamic and unpredictable conditions **Feedback:** VISUAL
Move to reach and dodge [The subject is asked to reach positive stimuli with forward, backward, and lateral steps while avoiding negative stimuli]	**Measure:** CoM control in dynamic and unpredictable conditions **Feedback:** VISUAL

TR Type B. Stroke patients will perform a home-based upper limb rehabilitation with the rehabilitation robot iCONE (Heaxel srl, Milan, Italy). Icone is a planar robot that enables the administration of upper limb neurorehabilitation protocols based on the intensive repetition of exercises defined by the clinical operator. The device integrates a computer with a multi-touch screen and dedicated management software for the provision of fully customizable, interactive exergames requiring the coordination of both shoulder and elbow to perform reaching tasks. During the exercise, the patient holds the ergonomic handle and moves it to reach some targets displayed on the screen, receiving real-time visual feedback about their position. During the session, the robotic system acquires both kinematic and dynamic data and uses the assessed motor performance to optimize the interaction

with the patient. Moreover, periodical reports are generated for both patients and the clinical staff, informing about performance with graphical and numerical indicators. The TR architecture allows for remote management of patient records, therapy settings, and reporting, making the robotic system suitable also for the patient's home or other non-hospital environments.[45] The therapy can be set up remotely by a clinical operator, while direct supervision can be provided by a non-clinical operator, such as a patient's family member.

Usual Care (UC). The UC group (active control group) will perform conventional rehabilitation exercises at home, with the same Frequency (4 sessions/week; 5 weeks) and Time (50 min/session) of the TR intervention. According to the disease, patients will perform two different UC protocols: UC Type A for MS and PD and UC Type B for post-stroke.

UC Type A. The UC intervention for people with PD and MS will be focused on standard motor exercise training aimed at muscle mobilization and strengthening. Exercises will be provided through digital support (digital booklet) to perform training at home according to MS and PD guidelines.[46,5] Researchers will provide patients with brief training on how to perform exercises, specifying the frequency and time of rehabilitation sessions. Moreover, patients will be invited to register the rehabilitation activities performed in a paper diary indicating, for each session carried out, the date of execution, the number of exercises performed, the time spent, and notes about any difficulties encountered during the exercise training.

UC Type B. The UC intervention for post-stroke individuals will primarily focus on the repetitive practice of exercises aimed to mobilize and enhance motor control of upper limb functions, contributing to improved joint mobility, postural control, muscle recruitment, and fine hand mobility.[47,48] Each patient will receive a set of exercises and a prescribed number of repetitions based on his/her individual upper limb motor deficits. The exercises will be thoroughly explained to the patients, and a visual aid, such as a picture book, will be provided to enhance comprehension and facilitate independent practice. Among the four weekly sessions, one will include supervision by a clinician to explain the tasks and adapt the treatment plan according to the patient's progress.

Outcome measures

Participants will undergo an extensive evaluation at the baseline (T0), post-intervention (T1), and at the follow-up (T2) (see Figure 1 "Study Period").

Primary outcome measure. The primary outcome will be the change in the perceived level of disability as measured by the World Health Organization Disability Assessment Schedule 2.0 (**WHODAS 2.0**[32] evaluated at each time point of evaluation (T0, T1, and T2). The WHODAS 2.0 questionnaire assesses the functioning and disability level in six domains (cognition, mobility, self-care, getting along, life activities, and participation in community activities) according to the International Classification of Functioning, Disability and Health (ICF). During the interview, participants are asked questions about the degree of difficulty that they experience in doing different daily life activities in relation to any health condition. Responses are assigned on a Likert scale ("none" = 1; "mild" = 2; "moderate" = 3; "severe" = 4; "extreme" = 5). The summary scores for the WHODAS 2.0 will be obtained through 3 steps: 1) summing of item scores within each domain; 2) summing all six domain scores; 3) converting the summary score into a metric ranging from 0 to 100 (where 0 = no disability and 100 = full disability).

Secondary outcome measures. Secondary outcomes will be the changes in cognitive and motor measures evaluated at each time point of evaluation (T0, T1, and T2).

Outcome measures common to all rehabilitation scenarios (PD, MS, and post-stroke). The global cognitive functioning will be evaluated in PD, MS, and post-stroke groups through the **Montreal Cognitive Assessment** (**MoCA**) test.[49] The MoCA test is a screening battery that also includes subtests to assess frontal functions such as set-shifting, abstraction, and cognitive flexibility (MoCA total score range: 0–30). High scores are indicative of better general cognitive performance.

As specific measures of visuo-perceptual and attentional abilities, the **Trail Making Test** (**TMT**) part A and B[50] and the **Symbol Digit Modalities Test** (**SDMT**)[51,52] will be administered.

The TMT is a neuropsychological test that involves visual scanning (TMT-A) and dual-task (TMT-B). In Part A, the participant must draw a line to connect consecutive numbers from 1 to 25. In Part B, the participant connects numbers and letters in an alternating progressive sequence, 1 to A, A to 2, 2 to B, and so on. The TMT is scored by how long it takes to complete each part of the test. Moreover, in order to measure executive functioning, the difference in time between TMT-B and TMT-A is calculated (TMT B-A). High execution times indicate poor performance.

The SDMT is a commonly used test to assess psychomotor speed. This paper-pencil measure involves a substitution task using a coding key with nine different abstract symbols, each paired with a numeral. Below the key, a series of these symbols is presented, and the participant is asked to write down the corresponding number for each symbol. The score consists of the number of correct substitutions within 90 s. Higher scores indicate better performance.

The **Beck Depression Inventory for Primary Care** (**BDI-PC**[53]) and the **State-Trait Anxiety Inventory – Form Y** (**STAI-Y**[54,55]) will be used to detect changes in depressive and anxiety symptoms, respectively.

The BDI-PC is a 7-item questionnaire with each item rated on a 4-point scale (0–3). It is scored by summing ratings for each item (range 0–21). Higher scores indicate greater deflection of mood tone.

The STAI-Y is a commonly used measure of trait and state anxiety (20 items for each). All items are rated on a 4-point scale (from "Almost Never" to "Almost Always"). STAI – Y2 is scored by summing ratings for each item (State-Anxiety: range 0–80; Trait Anxiety: range 0–80). Higher scores indicate greater anxiety.

As a measure of gross manual dexterity, the **Box and Block Test** (**BBT**)[56] will be administered in all groups. The BBT is composed of a wooden box divided into two compartments, one of which contains 150 blocks. The BBT administration consists of asking the patient to move, one by one, the maximum number of blocks from one compartment to another within 60 s. The score is based on the number of blocks transferred from one compartment to the other in 60 s. Higher scores are indicative of better manual dexterity.

Outcome measures common to PD and MS groups. The finger dexterity will be measured by the **Nine Hole Peg Test** (**9-HPT**).[57] Participants are asked to take 9 pegs from a container, one by one, and place them into the nine holes on the board of the test, as quickly as possible, using only the hand evaluated. The scoring considers the number of seconds taken by patients to complete the test or the number of pegs placed in 50 or 100 s. High execution times indicate poor finger dexterity.

The **modified Dynamic Gait Index** (**mDGI**)[58] and the **Mini-Balance Evaluation Systems Test** (**Mini-BESTest**)[59] will be used to evaluate changes in static and dynamic balance. In particular, the mDGI measures the capacity to adapt gait to complex tasks utilizing eight tasks and three facets of performance (gait pattern score [0 −3], level of assistance [0 −2], and time level score [0 −3]). The total task score (range 0–8) is calculated by summing the three performance facet scores for each task. Higher scores are indicative of better performance.

The Mini-BESTest aims to identify the disordered systems underlying the postural control responsible for poor functional balance. This tool is composed of 27 tasks (36 items in total) assessing biomechanical constraints, stability limits/verticality, anticipatory responses, postural responses, sensory orientation, and stability in gait. Each item is scored based on ordinal scale scoring from 0 to 3 where 3 = best performances and 0 = worst performances. The total score is provided as a percentage. Higher scores are indicative of better performance.

Changes in the perceived stability during activities of daily living will be measured with the **Activities Balance Confidence scale** (**ABC**[60,61]) a 16-item questionnaire that measures an individual's confidence during activities without falling or experiencing a sense of unsteadiness. Each item is scored ranging from 0 to 100. Higher scores are indicative of higher perceived stability.

Outcome measures specific for MP, SM, or post-stroke group. The **Movement Disorder Society - Unified Parkinson's Disease Rating Scale** (**MDS-UPDRS**)[62] part III will be administered in PD patients to assess changes in motor functionality. Part III (''motor examination'') is composed of 18 items scored using a 5-point ordinal scale where 0 = "normal", 1 = "slight", 2 = "mild", 3 = "moderate", 4 = "severe". Higher scores indicate increased severity. According to Jankovic,[63] we will calculate 4 MDS-UPDRS III subscores: tremor (range 0–40 points), rigidity (range 0–20 points), bradykinesia (range 0–52 points), and Postural instability (range 0–20 points) subscores.

The **Expanded Disability Status Scale** (**EDSS**)[64] will be administered to MS patients to evaluate changes in their level of disability. It provides a total score on a scale that ranges from 0 to 10 in 0.5-unit increments. Higher scores indicate higher levels of disability.

The **Fugl-Meyer Assessment – Upper Extremity** (**FMA-UL**)[65] and the **Action Research Arm Test** (**ARAT**)[66] will be administered to assess the sensory-motor functions of the upper limb only in post-stroke patients. Specifically, the FMA-UL, a stroke-specific, performance-based impairment index, will be used to assess the motor functioning of the upper limb. Scoring is based on direct observation of performance. Items are scored using a 3-point ordinal scale where 0 = cannot perform, 1 = performs partially, and 2 = performs fully. The total possible motor score for the upper extremity is 66.

The ARAT is a 19-item measure assessing the upper extremity performance (coordination, dexterity, and functioning). Items are scored using a 4-point ordinal scale where 0 = "no movement", 1= "movement task is partially performed", 2 = "movement task is completed but takes abnormally long", and 3 = "movement is performed normally". Scores range from 0 to 57 points with higher scores indicating better performance.

Other outcomes. Brain **Magnetic Resonance Imaging (MRI)** data will be collected at each time-point of evaluation on a Siemens Prisma 3.0 T scanner (optional evaluation). Specifically, structural connectivity data will be collected using DWI (Echo planar imaging (EPI) multi-shell DWI, 5 b0 images, 50 encoding directions with b = 1000 s/mm^2 and 50 with b = 2000s/mm^2 TR = 3600 ms, TE = 92 ms, 2 mm^3 resolution, 72 slices). Moreover, functional connectivity will be explored with a resting state functional MRI sequence (TR = 2570 ms, TE = 15/34/54 ms, matrix size = 64 × 64 × 31, resolution = 3.75 × 3.75 × 4.5 mm^3, 200 volumes).

Data collection

Demographic characteristics and the level of the technological expertise of patients will be collected at the baseline

evaluation (T0); data from participation, clinical, functional, and motor measures (primary and secondary outcomes) will be collected by blinded examiners/assessors at each time-point of evaluation (T0, T1, T2); to ensure that patients follow the prescribed intervention, paper diaries will be used in the UC group to record the date of execution, the number of exercises performed, the time spent, and any difficulties encountered during the exercise training. In contrast, the TR group will have their adherence automatically collected through the digital platform; finally, data on the usability and acceptability of the technological solutions and safety of interventions will also be collected post-intervention (T1). Specifically, the technological systems usability will be evaluated with the System Usability Scale (**SUS**),[67] the technological acceptability as measured by the Technology Acceptance Model (**TAM**)[68] in PD, MS, and post-stroke patients, while the safety issues (i.e., adverse events related to the intervention throughout the study duration) with "ad-hoc" clinical questionnaire. Finally, data on adherence to the rehabilitative program and performance levels at rehabilitation exercises will be automatically collected through a TR platform.

Statistical analysis

Statistical analyses on outcome measures will be conducted using Jamovi 2.2[69] (https://www.jamovi.org). Descriptive statistics of the sample will include frequencies for categorical data, median and interquartile range (IQR) for ordinal variables, and Mean and Standard Deviation (SD) for continuous measures. The assumption of normality will be checked by the Shapiro-Wilk test for continuous variables. We will investigate statistically significant after-treatment changes in primary and secondary outcome measures according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. An Intention-to-treat approach will be carried out to address missing data. A treatment effect (TR vs. UC) will be investigated through repeated measures ANOVA. Moreover, a score modification at follow-up (T2, 2 months after treatment) in both groups will be evaluated by means of regression analyses over time considering previous values at baseline and T1.

Discussion

The increasing demand for rehabilitation among people with neurological conditions claims the identification of innovative digital solutions able to enhance access to rehabilitation services while promoting quality-of-life, clinical, and functional outcomes. Results from the present RCT will inform about the usability, acceptability, safety, and efficacy of TR protocols with digital (Homing) and robotic (iCONE) tools in reducing the perceived level of disability in post-stroke, PD, and MS patients.

The reason for choosing Homing and iCONE ("pros") is that they are designed to enhance an intensive rehabilitation program with task-oriented exercises. The task-oriented training is a well-known rehabilitation approach that can have a positive impact on recovery by enhancing brain plasticity after brain injury or neurodegeneration. Moreover, intensive multisensory rehabilitation is particularly effective, but it requires a high level of commitment from both patients and physiotherapists, resulting in high costs for the healthcare system.

Overcoming these obstacles to rehabilitation can be challenging, but these two systems offer ways to help. iCONE and Homing systems allow for controlled and customized task-oriented exercises based on the unique characteristics of each patient at home. Screens and visual/auditory feedback provide sensory input, promoting learning and engagement through the interactive nature of the technological device. Furthermore, both iCONE and Homing are cloud-based systems, allowing the clinical staff to manage remotely the rehabilitation intervention. Finally, these technological systems are ease transportable, permitting their use across various settings including the patients' home or other non-hospital environments. It's worth highlighting that one of the major "cons" of telerehabilitation could be represented by the inability of the therapist to act in case of symptoms and adverse events and providing the patients with some home-based solutions to monitor vital parameters during the rehabilitation protocol could be important to promote safety during the telerehabilitation session (and after it). Future steps of development could integrate the system with digital devices for telemonitoring.

We expect that TR protocols will be both usable and acceptable for people with CNDs in line with previous data.[10,17,18,22] It is well known that TR can serve as a powerful tool to strengthen rehabilitation in primary health care increasing access to care and overcoming barriers. TR has proven to be useful and effective for patients with NCD during the lockdown period due to the SARS-CoV-2 pandemic but should become a constant asset to ensure continuity of care from the clinic to the patient's home.[70] The adoption of digital and robotic technologies within the TR approach will allow for overcoming accessibility and cost barriers and scaling up rehabilitation services to patients in need from the early stages of the disease.

The flexibility that characterizes TR protocols will allow people with CNDs to freely choose when to complete each daily rehabilitation session in relation to their preferences and daily needs and routines. This option increases the engagement and compliance of patients, promoting the achievement of health and quality of life outcomes.[71]

In addition, we expect that the TR approach will determine several positive effects on quality of life, reducing the perceived level of disability. Our previous studies in the field showed that the TR approach with digital or robotic tools ensured the continuity of care in people with

CNDs, with high levels of adherence to treatment,[10,11,13,17] short- and long-term beneficial effects on both motor and non-motor abilities,[11,13,17,19,20,23,28] and improved quality of life domains such as participation and autonomy in daily routine.[10,11,13,17,19,23]

This study is not without limitations. We recognize that technical problems such as the lack of internet connectivity and insufficient space for motor exercises at home may hinder the availability of TR treatment. Additionally, the follow-up evaluation period is relatively short due to study constraints.

Conclusion

The implementation of TR protocols with robotics and digital tools, developed and validated with an evidence-based approach, will enable a more targeted and effective response to the growing need for rehabilitation linked to chronic neurological conditions. We expect that the flexibility that characterizes the TR protocols will promote the motivation and engagement of patients in their continuum of care, enhancing adherence to treatment and the achievement of health and quality-of-life outcomes. Future steps of implementation could integrate the technological platform with digital devices for telemonitoring. This will enable real-time tracking of vital parameters (e.g., blood pressure and heart rate) for each patient, along with performance data and treatment adherence. Such integration will allow for better monitoring of safety during the rehabilitation sessions.[72,73]

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