

DANCE Rehabilitation EXperience (DANCEREX-DTx): Protocol for a randomized controlled trial on effectiveness of digital therapeutics in chronic neurological disabilities

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Abstract

Objective: Rehabilitation is an important player in preventing and reducing the high impact of disability on everyday functioning in chronic neurological diseases (CNDs), especially if timely, intensive, and multidimensional. However, to date, rehabilitation is often a service accessible only to a few people, and the issue of a progressive decrease in treatment adherence still remains to be addressed. This study protocol describes an RCT whose aim is to test the effectiveness in terms of adherence of DANCE Rehabilitation EXperience (DANCEREX-DTx), a new digital therapeutic solution which combines a holistic, multidimensional program based on dance and music with an innovative motivational system.

Methods: The randomized, single-blind, controlled trial will involve 192 patients with CNDs from three rehabilitation centers in Italy. Participants will be randomized (with an allocation ratio of 2:2:1) into three interventions: (1) DANCEREX treatment, (2) multidimensional dance-based program, and (3) educational program. Groups will be assessed at the baseline (T0), after intervention (T1—after 12 weeks), and after six months from enrollment (T2). The primary outcome will be treatment adherence in terms of the number of drop-outs and the percentage of attended sessions on the total prescribed. Moreover, a multifaceted evaluation, including quality of life and clinical/functional measures, will be conducted at each time-point. Surrogate measures (neuroimaging and neurobiological) will be collected at T0 and T1. Finally, usability and acceptability will be assessed at T1.

Results: We expect the validation, in terms of usability, acceptability, and effectiveness of DANCEREX-DTx as an innovative rehabilitation program able to respond in a sustainable way to the great need for rehabilitation of people with CNDs.

Conclusion: With DANCEREX-DTx, we aspire to change the hospital-centered paradigm of rehabilitation care to bring it to the patients' homes, making them active in their treatment path and promoting motivation and adherence to treatment from the initial stages of the disease.

Trial registration: The trial was registered in the clinicaltrials.gov database (identifier NCT06112639) on 2023-11-01.

Keywords

Rehabilitation, multiple sclerosis, dementia, digital therapeutics, motivation

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Background and rationale

Chronic neurological diseases (CNDs) appear the second most impactful clinical condition that needs timely rehabilitation^{1–3} to counteract the neurodegenerative process.^{1,4} Physical therapy and cognitive activities have been shown to have neuroprotective effects,⁴ attenuating chronic neuroinflammation which has a critical role in most CNDs and in promoting brain plasticity.^{5,6}

For rehabilitation to be impactful in the context of CNDs, it must be characterized by high intensity and grounded in multidimensional approaches.^{1,7} Timeliness is also particularly critical in neurodegenerative disease of ageing since these patients are usually diagnosed and treated only after symptoms appear, that is about 10–20 years after the beginning of the pathological changes in the brain, thus making it very difficult to counteract the disease progression. Moreover, intensive rehabilitation is particularly suitable for people with neurodegenerative diseases who need repeated and prolonged rehabilitation cycles due to the chronic and progressive nature of the disease.^{7–9} Finally, the multidimensional feature appears critical in CND management since typical signs of this condition include cognitive, psycho-behavioral and motor dysfunctions with significant long-term impacts on everyday activities.¹⁰ Dance-based rehabilitation programs fulfill the multidimensionality requirement by combining sensory–motor exercises with music and cognitive engagement. Moreover, this approach has been proved to be effective in several neurological disorders in reducing a wide range of motor (e.g., endurance and falls), cognitive (e.g., memory, attention, executive functions) and psycho-behavioral symptoms.^{11–14} Neuroimaging research showed how dance can induce neuroplastic changes within a wide brain network, including both cortical and subcortical areas, targeting sensory, motor, communication, attention, memory, and emotional domains.^{6,11,12,15–17} However, the specific brain mechanisms involved are yet to be clarified.

Despite the need to intervene early to achieve clinical improvements, to date, rehabilitation is often seen as a disability-specific service accessible only to a few people and in moderate to advanced stages of the disease.¹ Therefore, new therapeutic solutions need to be advanced, able to scale up rehabilitation to reach all those in need and, at the same time, ensure treatment adherence. Recent data from the COVID-19 pandemic period indicate that healthcare professionals are inclined to efficiently adopt innovative digital ecosystems to ensure patients' effective management and ongoing care.¹⁸ Nevertheless, even with the integration of innovative solutions, the adherence rate to the treatment remains a crucial aspect of the rehabilitation program. Previous studies involving patients suffering from CNDs have shown that treatment adherence tends to decrease progressively over time, plausibly impacting the

efficacy of the program.¹⁹ This phenomenon is likely related to mechanisms of disengagement, which can reduce the effectiveness of the rehabilitation treatment. In this framework, new digital therapeutics can represent a disruptive factor in healthcare, capable of expanding the offer of rehabilitation care in a sustainable way for the National Health System. Several works showed that new technological solutions appear feasible, easily accepted, and effective frontier for the management of CNDs, able to provide continuous delivery of rehabilitation services and optimize the timing and intensity of the rehabilitation intervention.^{8,9,20} However, the issue of treatment adherence remains an open question to be addressed.¹⁹ To counteract the disengagement mechanisms underlying the decrease in treatment adherence, the rehabilitation program can be transformed into an experience that activates a holistic sense-making process capable of integrating the treatment into the patient's everyday routines of care. The rationale for this option is that at the core of motivation in performing an activity lies how such an activity is given meaning,²¹ which in turn depends on how it is categorized within one's own experience.²² For this reason, making sense of rehabilitation encompasses also how an activity is cognitively processed, within one's unique repertoire of cognitive categories and knowledge. At the same time, this network of categories is built up through motor and multimodal interactions with a specific activity, that is, through one's own experience of rehabilitation.²³ This transition from rehabilitation as a task to rehabilitation as an experience leads to the patient's enaction, that is, the patient's activation in making sense of rehabilitation as the motivational drive to ensure sustained adherence to the treatment.

Based on these premises, our research group has developed DANCE REhabilitation Experience (DANCEREX-DTx), a new digital therapeutic (DTx) solution delivered via a telemedicine platform which combines a holistic, multidimensional program based on dance with an innovative motivational system in the form of an applied game. DANCEREX-DTx started from previous experience developed during research and development projects^{24,25} financed by the Lombardy Region under the POR-FESR 2014–2020 program. It consists of a digital application that integrates two main components: a multidimensional dance-based program and a motivational system to promote patients' adherence, engagement, and motivation,^{24,26} which are crucial aspects when carrying out an intensive treatment to produce clinical benefits for the patient. To date, despite the literature showing the efficacy of digital intensive multidimensional rehabilitation treatment in CNDs, no data specifically related definition of the protocols, efficacy, and safety of DTx for the rehabilitation of people with CNDs are available.^{27,28}

The primary goal of this study is to illustrate the protocol of a randomized control trial that will be conducted to verify

the ability of DANCEREX in enhancing adherence to rehabilitation treatment, ameliorating quality of life and clinical outcomes, diminishing chronic neuroinflammation, and fostering neural plasticity in early stages of disease.²⁹

Methods

The protocol of the study has been prepared as outlined in the “Standard Protocol Items: Recommendations for Interventional Trials” 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.

Trial design and setting

This study was designed as a multicenter randomized controlled trial involving outpatients from rehabilitation units of three clinical centers in Italy: IRCCS Fondazione Don Carlo Gnocchi (Milan), IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (Brescia), and IRCCS Centro Neurolesi “Bonino Pulejo” (Messina). It was designed per Consolidated Standards of Reporting Trials (CONSORT) guidelines for pilot trials of nonpharmacological treatments. Before recruitment, all patients will be informed about the study, and informed consent will be obtained by the clinicians involved. Participants will be randomized (with an allocation ratio of 2:2:1) into three interventions: (1) DANCEREX treatment, (2) multidimensional dance-based program (MDBP), and (3) educational program. Study participation will be six months and will include three evaluations: T0 = baseline evaluation; T1 = assessment after the intervention (follow up at 12 weeks); T2 = assessment after six months from enrollment. The trial work plan is shown in Figure 2.

Sample size

The sample size was computed using the *G* Power 3* software.^{30,31} The sample size was estimated based on literature data relating to the primary outcome of this study, i.e. the percentage of patients who do not complete the rehabilitation program (drop-out rates). The study by Patterson and collaborators³² estimated the incidence of drop-out in standard treatment at around 44%. Based on previous experiences,²⁴ we estimated that the group treated with DANCEREX will have a dropout rate of 22% at the end of 12 weeks of treatment. Assuming a statistical power of 80% (Type I error rate of 0.05), and a 5% of possible drop-outs from magnetic resonance imaging (MRI) evaluation, a total of 192 subjects should be needed for this trial, with an allocation ratio of 2:2:1 respectively for the DANCEREX, MDBP and placebo groups.

Study population, recruitment, and randomization

According to the sample size calculation, the DANCEREX trial has a target enrollment of 192 outpatients affected by CNDs: MS ($N=96$) and pre-MCI (subjective memory complaints (SMC) or subjective cognitive complaints (SCC))/MCI at risk of AD ($N=96$). Eligible patients who meet all inclusion criteria (see the paragraph below) will be randomized using a web-based allocation concealment through a computer-based algorithm created by an independent statistician. Randomization will be stratified according to diagnosis (MS vs pre-MCI/MCI), age, sex, education, and disease severity (Expanded Disability Status Scale (EDSS) score for MS and Montreal Cognitive Assessment (MoCA) score for pre-MCI/MCI). Due to its nature, the trial intervention will not be blinded to clinicians or patients. Conversely, clinical endpoints and data collection from clinical/psychological questionnaires will be blinded for examiners/assessors. The statistician conducting the data analysis will be masked for the group allocation.

Inclusion and exclusion criteria

Inclusion criteria for all participants will be:

1. age between 18 and 85 years (adult and older adult);
2. education equal to or more than five years;
3. agreement to participate with the signature of the informed consent form;
4. clinical diagnosis of MS according to the 2017 revised criteria of MC Donald—(EDSS³³) score equal or less than 4.5,³⁴ R-R disease course, freedom from relapses, and steroid treatment for at least one month
OR
clinical diagnosis of pre-MCI (SMC and/or SCC)/MCI at risk of AD with the Clinical Dementia Rating (CDR³⁵) scale equal or less than 0.5; and
5. normal score to a screening test for cognitive impairment (MoCA test >15.5, cutoff score according to Italian normative³⁶).

Exclusion criteria will be:

1. presence of comorbidities that prevent patients from undertaking a safe home program (e.g., balance problems with clinical history of falls in the past six months and/or use of assistive devices for deambulation);
2. presence of overt hearing/visual impairment;
3. for the MCI group, the absence of a caregiver/study partner able to support the participant;
4. not living in one's own home;
5. for the MS group, a score in cerebellum function at EDSS³³ greater than 3; and
6. participation in other clinical trials and/or other rehabilitation treatments

STUDY PERIOD			
	Baseline	Post-allocation	
TIMEPOINT	T0	T1	T2
ENROLLMENT			
<i>Eligibility screen</i>	X		
<i>Informed consent</i>	X		
<i>Allocation</i>	X		
INTERVENTIONS			
<i>Multidimensional dance-based program</i>	◀────────────────▶		
<i>Educational program</i>	◀────────────────▶		
<i>DANCEREX-DTx</i>	◀────────────────▶		
ASSESSMENTS			
<i>Demographic and clinical characteristics</i>	X		
<i>Technological Assessment</i> Technological Expertise System Usability Scale User Experience Questionnaire Intrinsic Motivation Inventory- Interest/Enjoyment subscale Technology Acceptance Model 3	X	X	
<i>Primary outcome</i> Adherence	◀────────────────▶		
<i>Secondary outcome measure:</i>			
<i>Motor outcome measures</i> 6 Minutes Walking Test Mini-Best Test	X	X	X
<i>Participation and quality of life outcome measures</i> Positive and Negative Affect Scales Patient Activation Measure EQ-5D-5L Short Form Health Survey 36 Modified Fatigue Index Scale State-Trait Anxiety Inventory Beck Depression Inventory – PC	X	X	X
<i>Cognitive outcome measures</i> Montreal Cognitive Assessment verbal and semantic fluency Trail Making Test Stroop Test Free and Cued Selective Reminding Test 15-Words of Rey Symbol Digit Modalities Test	X	X	X
<i>Surrogate Measures</i> 3T Magnetic Resonance Brain Imaging Biomolecular markers	X	X	

Figure 1. SPIRIT figure for the schedule of enrollment, interventions, and assessments in the study design.

Note. T0: baseline assessment; T1: assessment after the intervention; T2: follow-up evaluation, after six months; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

*Only technological expertise will be collected at T0.

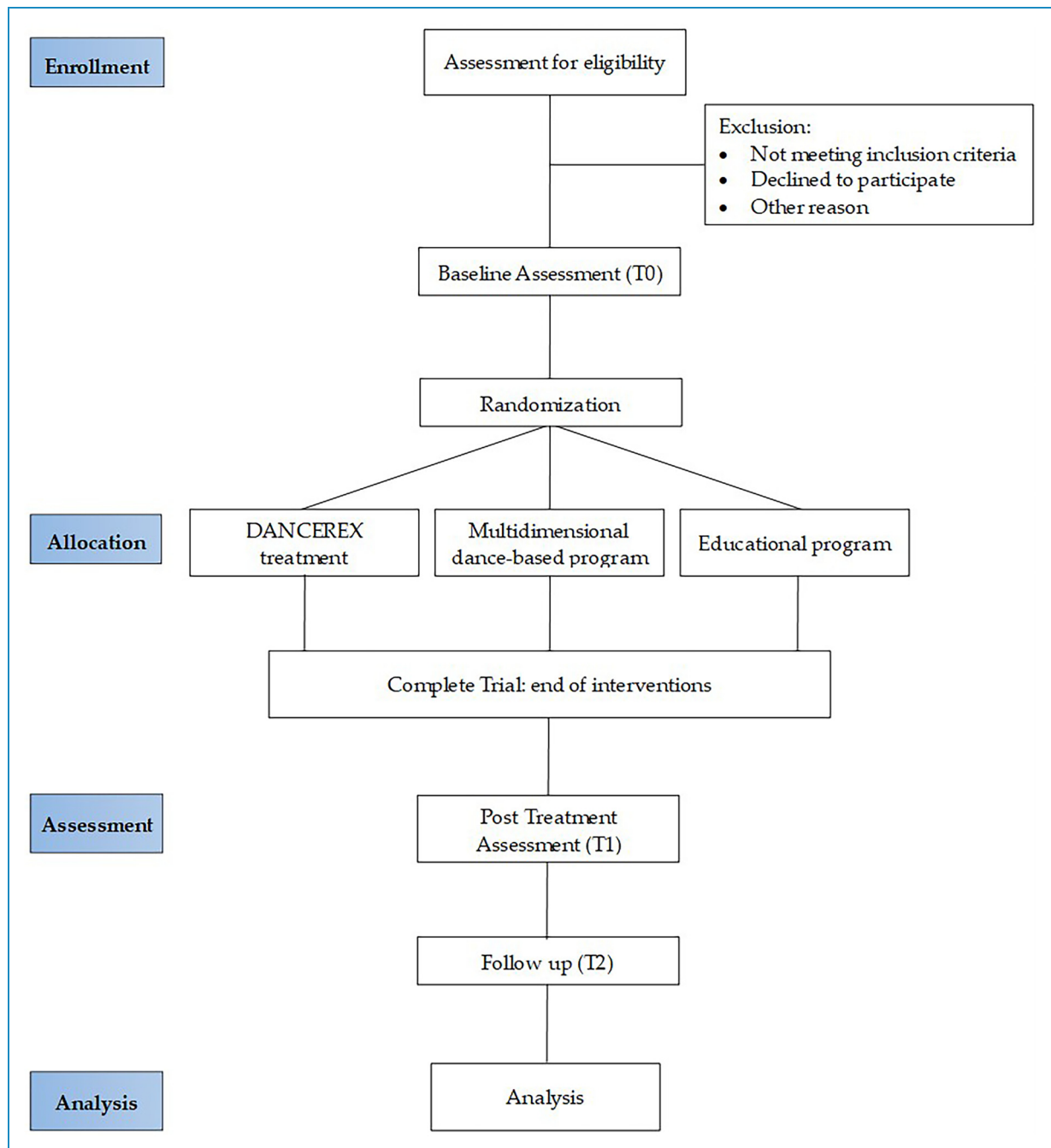


Figure 2. Trial work plan.

Trial interventions

The trial protocol provides for the random allocation of participants (ratio 2:2:1) to three different groups: (1) DANCEREX treatment, (2) multidimensional dance-based program, and (3) educational program. For each group, the treatment will last 12 weeks with a frequency of two sessions a week, each lasting 45–60 min. Patients will be provided with a preset tablet with a mobile internet connection on which they log in and visualize the activities prescribed

for the day. At baseline, all participants will receive a training session on the use of the tablet device and the specific app of the treatment, and a user manual.

1. **DANCEREX** (experimental treatment—dance with motivational support): the treatment proposed through the DANCEREX will be delivered using the DTx model: the app will include the same dance-based exercises and scheme of the MDBP (two sessions/week for

12 weeks, see next paragraph for further details) integrated into a digital formulation (i.e. an applied game). In addition, the DANCEREX app involves a game dynamic in which the execution of the rehabilitation sessions “feeds” a digital book that allows the rehabilitation experience to be placed in a narrative context. In other words, DANCEREX integrates the dance activities with an interactive digital novel providing experiential affordances embedded in the narrative design and modeled in gameplay out of the completion of dance activities to evoke a holistic sense-making process of the patient journey in managing one’s condition in everyday routines. To trace participants usage of the DANCEREX, the app is integrated into a digital medicine telerehabilitation platform (MAIA-connected care <https://www.maiacconnectedcare.it/>).

2. MDBP (active control group—control treatment with dance): the treatment will last 12 weeks with a frequency of two sessions a week, each lasting 45–60 min. It will be provided via a digital medicine telerehabilitation platform (MAIA-connected care <https://www.maiacconnectedcare.it/>). The patient will perform the exercises (different dance styles, i.e. Irish Dance, Hip Hop, Cha Cha Cha) independently at home using videos that illustrate the activity to be performed for each treatment session on a mobile device (tablet). The intensity of the exercise will be moderate with a progressive increase in difficulty level over the weeks. The treatment will start with simple dance movements to be performed in a sitting position to proceed with gradually more complex sequences, always to be performed in safe conditions (first seated and then standing, holding onto a chair).
3. *Educational treatment* (placebo group—no treatment group): subjects will view educational/informative videos on managing of their clinical condition on a tablet. The treatment will be provided via a digital medicine platform (MAIA-connected care, <https://www.maiacconnectedcare.it/>). The digital content of this program will focus on five topics composing the S.A.M.B.A. acronym: Socialization, environmental factors, Movement, psychological well-Being, and Alimentation.

In all three groups, data about rehabilitation sessions (e.g. when, if and how the exercises will be performed) will be automatically recorded on personal account of the patient on the telerehabilitation platform. Each rehabilitation session is divided in phases, at the end of each phase the patients are requested to interact with the tablet to proceed, and each interaction is recorded on the platform. The researcher can visualize all these recorded interactions on the platform. Each session has an expected duration, and the system is able to calculate the effective duration of the session.

Outcome measures

Participants will undergo an extensive multidimensional and instrumental evaluation at the baseline (T0) and at each time point of evaluation (T1, T2) (see Figure 1 for more details).

Demographic and clinical characteristics

1. Demographic data: age, education, and sex
2. Clinical data: disease onset and duration, EDSS,³³ CDR,³⁵ drug therapy.

Primary and secondary outcome measures. To test patient-relevant structural and procedural effect, the adherence to treatment, in terms of both numbers of drop-out and percentage of attended sessions on the total prescribed, will be considered as the primary outcome measure of the study.

Moreover, the secondary outcome measures will be:

1. Change in cognitive domains measured by:
 - (a) MoCA:³⁶ a screening test for global cognitive functioning. It includes tasks involving several domains: visuospatial/executive function tests, naming, selective and sustained attention, language, abstraction, memory, and orientation.
 - (b) Verbal and semantic fluency:³⁷ a measure of verbal and semantic fluency abilities, executive functions abilities—lexical store size, lexicon access, and lexical organization.
 - (c) Trail making test (Part A and B):³⁸ a measure of attentional abilities, visuoconceptual and visual-motor tracking. Part A involves visual scanning, number recognition, number sequencing and motor speed. Part B assesses mental flexibility in managing more than one stimulus at a time and in shifting the course of an ongoing activity;
 - (d) Stroop test:^{39,40} a measure of executive abilities, including visual attention, selective attention, cognitive flexibility and inhibitory control of behavior.
 - (e) Free and cued selective reminding test:⁴¹ a measure of long-term episodic verbal memory.
 - (f) 15-Words of Rey:⁴² a measure of long-term episodic verbal memory.
 - (g) Symbol digit modalities test:^{43,44} a measure of attention and processing speed.
2. Change in motor domains measured by
 - (a) 6 minutes walking test, a general indicator of overall physical performance and mobility measuring the distance covered by walking over 6 min.⁴⁵
 - (b) Mini-balance evaluation system test (mini-BESTest):⁴⁶ a 14-item scale that evaluates balance. Items are grouped into four subcomponents: anticipatory postural control, reactive

postural control, somatosensory orientation, and dynamic walking.

3. Change in participation and quality of life domains measured by patient-reported outcome measures—battery involving:
 - (a) Positive and Negative Affect Scales:⁴⁷ self-report questionnaire involving two mood scales: one for person's positive emotions and the other scale for negative (10 emotions for each).
 - (b) Patient activation measure:⁴⁸ a 13-item scale that assesses a person's underlying knowledge, skills, and confidence integral to managing their health and healthcare. Individuals in the highest activation level are proactive with their health, have developed strong self-management skills, and are resilient in times of stress or change.
 - (c) EQ-5D-5L (The EuroQol Group, 1990:^{49,50}) a measure of health status consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on five levels of difficulties (from no to extreme problems). Moreover, the questionnaire involves a visual analog scale recording the patient's self-rated health.
 - (d) Short Form Health Survey 36 (SF36):⁵¹ short scale on health status, consisting of 36 questions subdivided into eight scales: Physical Function, Physical Role, Body Pain, General Health, Vitality, Social Function, Emotional Role, and Mental Health.
 - (e) Modified Fatigue Index Scale:⁵² it identifies physical, cognitive, and psychosocial components of fatigue.
 - (f) Beck Depression Inventory for Primary Care,⁵³ a seven-item questionnaire for depressive symptoms.
 - (g) State-Trait Anxiety Inventory-Form Y^{54,55} for trait and state anxiety level (40 items).

Surrogate outcome measures: MRI and biomolecular indices (only at T0 and T1). Neural changes in structural and functional connectivity will be measured by 3T MRI. A harmonized multicenter protocol according to RIN-neuroimaging network guideline⁵⁶ will be adopted and these images will be collected: (1) T1weighted 3D images (minimum voxel size $1 \times 1 \times 1 \text{ mm}^3$) to assess changes in brain morphometry; (2) FLAIR 3D images to assess lesion load/to perform lesion segmentation at baseline; (3) DWI sequences (at least 30 diffusion-encoding directions with double-shell $b = 1000 \text{ s/mm}^2$; $b = 2000 \text{ s/mm}^2$) to detect changes in structural connectivity; (4) resting-state fMRI (at least 200 volumes) to assess brain functional connectivity pre-versus posttreatment; (5) 3D axial GRadient Echo, T2*w, 8 TEs, TE1/ Δ TE = 5.6/5.6 ms, time of repetition, TR = 51 ms, spatial resolution = $1 \times 1 \times 1 \text{ mm}^3$, flip angle, FA =

18° , acquisition time ~9' to assess quantitative susceptibility mapping.

Changes in biomarkers of neuroinflammation and neurodegeneration will be also evaluated at the biomolecular level, moving from previous results from our group. Specifically, imbalance in innate or adaptive immune response in neurodegenerative disease as MS^{57–59} and MCI/AD^{60–62} was found and specific biomarkers of disease progression (or prognostic biomarkers) were derived. Moreover, as previously shown, rehabilitation plays a role in reducing inflammation in MS⁶³ and sarcopenic patients^{64,65} during recovery, in less than six months' time-frame. These mechanisms involve the sympathetic nervous system and hypothalamic-pituitary axis with release of catecholamines, glucocorticoids, and serotonin^{66–68} and upregulation of the BDNF gene in the brain.⁶⁹ According to these premises, the following markers will be measured: (1) inflammatory cytokines (TNF, IL1 β , TGF- β , IL-6, IL-33, IL-8) and antiinflammatory cytokines (IL-10, IL-37); (2) protein associated to downstream inflammasome activation such as IL-18, active-caspase-1 (p20 kDa) for canonical NLRP3 activation and caspase-4,5,8 for noncanonical NLRP3 activation; (3) neurotrophic and neuroendocrine factors such as BDNF, catecholamines (dopamine, noradrenaline, and adrenaline), serotonin, cortisol, acetylcholine and β -endorphins; (4) neurodegenerative marker such as neurofilament-light chain. The serum of all enrolled subjects will be collected, centrifuged, stored, frozen at -8°C , and shipped (when necessary) to the sample-processing center (Laboratory of Molecular Medicine and Biotechnology of IRCCS Fondazione don Carlo Gnocchi ONLUS) according to harmonized SOPs. The serum will be measured by Enzyme-Linked ImmunoSorbent Assay and by Automated Immunoassay System.

Technological assessment

1. Technological expertise will be measured by ad hoc questionnaire at T0;
2. Usability will be measured by the System Usability Scale⁷⁰ at T1;
3. User experience will be measured by User Experience Questionnaire⁷¹ and Intrinsic Motivation Inventory—Interest/Enjoyment subscale⁷² at T1;
4. Acceptability of treatment will be detected by Technology Acceptance Model 3⁷³ at T1.

Data collection

Demographic and clinical characteristics will be collected at the baseline evaluation (T0); Data on adherence to the rehabilitative program (primary outcome) will be automatically collected through a digital medicine platform. Data from clinical/functional measures (secondary outcomes)

will be collected by blinded examiners/assessors at the baseline (T0) and at each time-point of evaluation (T1, T2). Surrogate measures will be collected by blinded assessors at baseline (T0) and after rehabilitation (T1). Moreover, adverse events related to intervention throughout the study duration will be recorded. Finally, additional data useful for a technological evaluation will be collected by validated questionnaires.

Data entry will be performed in a REDCap database by two assessors working together to ensure quality. Data monitoring will be ensured by the internal Clinical Trial Unit of FDG.

The informed consent form specifies data sharing procedures as well as measures to ensure confidentiality and the protection of personal information.

Statistical analysis

Descriptive statistics of the sample will include frequencies, median and interquartile range for categorical 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 changes in primary and secondary outcome measures according to the CONSORT guidelines. Within each clinical condition, treatment effects will be analyzed in relation to clinical, MRI and neurobiological data using a mixed model with random intercepts considering group, time, and Group $\times$ Time interaction. Least square means estimates will be used for between-group comparisons and treatment effects within each group during the observation interval. Two main analyses will be conducted: “intention to treat” and per-protocol analysis. The imputation of the missing data will be performed through the general linear model using the maximum likelihood method “full maximum likelihood.” The type 1 error will be considered equal to 5% ($\alpha = 0.05$) with a two-tailed analysis. The Jamovi software will be used for analysis.

Neuroimaging data analyses: the MRI data will be analyzed to identify the neuroplasticity mechanisms linked to functional recovery and cerebral structural reorganization linked to rehabilitation treatment. MRI data will be analyzed on three different levels: (1) at the level of fundamental units of the network (i.e. by evaluating the functional activation of the individual brain areas belonging to the network and the microstructural integrity of bundles of white matter that connect these areas); (2) at the level of relationship between pairs of nodes (brain areas) through the study of functional connectivity and structural connectivity; (3) at the level of topological properties of the network through the calculation of indices deriving from the graph theory such as the efficiency and segregation index. Furthermore, the correlation between neuroimaging and behavioral data will be performed. These analyzes

will allow to identify group-specific changes related to the intervention and to identify the brain areas involved in the structural and functional changes related to the behavioral changes (outcome measures).

Discussion

In the last years, the demand for rehabilitation services has doubled, and the need for rehabilitation currently accounts for about 2.41 billion individuals.¹ This worldwide phenomenon urgently requires new solutions to reach all people in need. In this context, digital health medicine is an ideal candidate, but like a new drug, these digital medical solutions will require rigorous validation adopting RCT designs.⁷⁴ The present RCT is designed to test the effectiveness of DANCEREX-DTx, an innovative rehabilitation software that integrates a holistic, multidimensional dance-based program with innovative motivational support for changing patient behavior to improve physical and mental activity in CNDs.

DTx, by definition, delivers evidence-based therapeutic interventions to prevent, manage, or treat a medical disorder or disease (DTx Alliance, 2020; www.dtxalliance.org), and clinical evidence and real-world outcomes are required for all DTx products. We expect that the findings of the RCT will result in a recommendation for using DANCEREX-DTx as a usable, safe, and effective way to change CNDs’ behavior patterns while improving physical and mental activity and triggering mechanisms at the neurobiological level. Rehabilitation is currently a treatment reserved for patients in the moderate and advanced stages of the disease. However, the need for rehabilitation in the context of CNDs is very relevant to the necessity for intensive and long-term treatments also in the initial stages of the disease. With DANCEREX-DTx, we aspire to foster the rehabilitation care and to bring it to the patients’ homes, making them active in their treatment path and promoting motivation and adherence to treatment from the initial stages of the disease. Accordingly, we hypothesize that treatment with DANCEREX in the early stage of the disease will be able to determine positive effects in terms of treatment adherence and in relation to clinical-disease difficulties. In more details, our expectation will be three-folded.

Firstly, we will expect a greater adherence to DANCEREX rehabilitation treatment compared to the other treatment. The motivational component of DANCEREX-DTx will support the achievement of clinical outcomes by making sense of the prescribed rehabilitation activities as a holistic experience, turning adherence to treatment into its integration into their daily care experience.

Moreover, a noninferiority effect on secondary outcome measures of DANCEREX with respect to MDBP and its superiority compared to educational treatment will be also

expected. In detail, we expect that patients with MS improve in terms of walking endurance, fatigue, strength, postural control, and balance.^{75–77} On the other hand, we assume that subjects with MCI show an improvement in cognitive functioning, particularly in memory and executive functions such as processing speed.^{78,79}

Finally, we expect to understand the mechanisms underlying the treatment-induced behavioral change at neural and biomolecular level. Indeed, although the benefits of dance-based treatments have been described in MS and neurodegenerative diseases,^{6,12,15–17} the brain mechanisms involved are not yet known. Moreover, we expect rehabilitation in the initial stages of the disease is able to slow down the evolution of disease processes (neuroinflammation and neural damage) by acting on various neurobiological mechanisms that cause neurodegeneration.⁸⁰ Previous evidence showed, in fact, how physical exercise can promote neuroplasticity and brain connectivity in the motor and cognitive circuits of neurodegenerative pathologies and, at the same time, attenuate chronic neuroinflammation by acting on neurotrophic factors such as the BDNF.^{5,81,82} Finally, understanding the mechanisms underlying the functional and structural modifications of the brain through the study of magnetic resonance will allow the opening of new avenues in individualized treatment planning.

Conclusion

To summarize, DANCEREX-DTx integrating a dance-therapy program with a motivational system could represent an ideal solution to provide an intensive early-rehabilitation program. Encouraging patient engagement and promoting “Do-It-Yourself” practices could be ideal solutions to sustaining treatment adherence and transforming daily care routines, which are crucial for long-term clinical efficacy. DANCEREX-DTx may be a promising, innovative, and sustainable digital solution that can facilitate the actual transfer of care from severe to early stage of CNDs. The development of the DANCEREX-DTx will enable more sustainable rehabilitation management, positively impacting the National Health Systems and patient care. The application of digitalized systems aligns with the World Health Organization’s call for a transformative approach to delivering rehabilitation treatments. This aims to reach a greater number of individuals, including those at home, without increasing the burden on hospital facilities.

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Authors’ contributions: Ba.F. and A.M.P. developed the original concept of the trial; Ba.F., Bo.F., B.V., R.O., A.M.P., M.F., C.M., M.R., C.E., L.B.V., M.S., and M.P.A. developed the design and methodology; S.M., T.P.D., A.M., Bo.F., and B.V. developed the analysis plan; Ba.F., Bo.F., B.V., and R.O. adapted the trial

proposal as a protocol paper; and Ba.F., Bo.F., B.V., and R.O. did manuscript writing. All authors reviewed and commented on drafts of the protocol and paper. All authors read and approved the final manuscript.

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Ethics approval and consent to participate: The study has been approved by the Ethics Committees of IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy; IRCCS Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy; and IRCCS Centro Neurolesi Bonino Pulejo, Messina, Italy. The study was registered as a clinical trial on clinicaltrials.gov (identifier NCT06112639). Eligible participants will be fully informed of the aims and procedures of the project. A reporting procedure will be in place to ensure that any serious adverse events are reported to the chief investigator. Informed written consent will be obtained from all participants before the study initiation.

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