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Effectiveness of two different exergaming systems in addition to conventional treatment for physical therapy in patients with multiple sclerosis: A study protocol for a multicenter, assessor-blind, 24-week, randomized controlled trial

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Abstract

Objectives: The main aim is to evaluate and compare the effectiveness of two specific exergaming systems in addition to conventional treatment on improving physical functional capacity, balance, muscle strength, spasticity in lower limbs, and quality of life in patients with multiple sclerosis. The secondary aim is to compare the effectiveness of each exergaming system to isolated conventional treatment.

Design: A multicenter, assessor-blind, 24-week, randomized controlled trial.

Methods: 39 patients diagnosed with multiple sclerosis will be allocated to three groups. A control group will perform a conventional treatment based on daily routine activities and/or combined training, whereas the experimental groups will be randomly divided to develop an active videogame-based exercise program through Nintendo Ring Fit Adventure© or Nintendo Wii Fit©, in addition to the conventional treatment. Study outcomes will be assessed at baseline and at 12 and 24 weeks. One-way ANOVA or Kruskal–Wallis tests will be used to analyze differences between groups at baseline and mixed ANOVA for differences between-within groups over time.

Discussion: The findings from this evidence-based trial, which includes both Nintendo© active videogames, could potentially establish exergame training as a valuable and reliable therapeutic tool for neurorehabilitation. It is essential to consider the customization, specifically in our case, on each multiple sclerosis condition, and ensure patients' adherence to the treatment.

Keywords

Multiple sclerosis, exergaming, exercise, physical therapy, neurological rehabilitation

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease of autoimmune nature and variable course, which produces demyelination and axonal damage in the brain and spinal cord.[1–3] Approximately, there are 2.8 million (35.9/100,000) people with MS (PwMS) worldwide,[3] consequently this pathology is considered as the

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most common cause of nontraumatic neurological disability in young adults.[4] Currently, there is no cure for this diagnosis, so rehabilitation focuses on long-term symptoms' management and exacerbation prevention to protect against progression.[2]

Recently developed neurorehabilitation therapies such as non-immersive virtual reality (VR) exergaming suggest favorable effects on functional outcomes.[5] In this context, videogame commercial consoles such as Nintendo Wii©[5,6] or Nintendo Switch©[7,8] have already been used as an alternative treatment to achieve a high level of functional independence and motor control through motivation, multimodal tasks, and continuous feedback with a virtual environment.[9]

Background

MS pathology is characterized by a progressive deterioration of the myelin sheath, leading to damaged neuron axons and cell bodies of the central nervous system.[1–3] The origin of MS is unclear due to the limited understanding of the disease etiology,[10] although a mixture of genetic, environmental, and lifestyle were identified as risk factors for MS development.[10,11] According to the disease development course, four MS subtypes can currently be diagnosed by the 2017 McDonald criteria[12]: relapsing-remitting MS, primary progressive MS, secondary progressive MS, and clinically isolated syndrome.[2,3,11,12] Despite the four subtypes, MS is known as the disease of "1000 faces" based on the variety and intensity of the symptoms that can arise unexpectedly.[13] The most common symptoms are fatigue, dizziness, visual disturbance, sensorimotor disorders, bladder and sexual dysfunctions, cognitive problems, imbalance, or functional impairments.[1–3,13] In this regard, the majority of PwMS are affected by relapsing-remitting MS (85%) suffering from continuous attacks that over time imply constant partial recoveries. In consequence, a significant detrimental impact has been demonstrated on disability, socioeconomic status, and quality of life, highlighting the need to develop effective treatments and rehabilitation options.[14]

The present literature provides an overview of the effectiveness of rehabilitation therapies for PwMS, including multidisciplinary rehabilitation, physical therapy, occupational therapy, cognitive and memory rehabilitation, dietary intervention, telerehabilitation, information provision, and spasticity management, among others.[15] A multimodal approach treatment review reported significant evidence of improvements in participation and self-care levels, sphincter control, mobility, and locomotion.[16] Additionally, physical therapy reviews, through different exercise programs (endurance, muscle power, task-oriented, mixed training, or others) compared with no-exercise therapy reported benefits to muscle power, exercise tolerance and mobility-related activities, health-related quality of life, and fatigue.[17,18] In this regard, current guidelines for the application of various training modalities (resistance, endurance, and combined)[19] emphasize the need to individualize exercise prescription in accordance with each participant's characteristics and health profile, especially considering the severity of the symptoms and the Expanded Disability Status Scale score.[20]

Current literature has shown advances in the treatment of people with neurological diseases, for example, both VR training and telerehabilitation being useful complements to conventional therapy.[21] Among different VR modalities, non-immersive VR exergaming is considered an inexpensive and motivational therapeutic alternative that could be played at home, alone or with others.[22] In addition, existing literature on MS exergaming suggests positive impacts on balance,[23,24] physical and cognitive abilities, as well as psychosocial status and fatigue.[25] In this field, Nintendo Wii Fit© (NWF) has been one of the most used exergame tools in the last decade for balance and gait outcomes,[26–28] including specific MS trials.[29–32] However, the current Nintendo trending exergame is Nintendo Ring Fit Adventure© (NRFA), an active videogame that is similar to NWF but in this case using an interactive fitness circle (Nintendo Ring-Con©) instead of a balance board device (Nintendo Balance Board©) that works as a motion sensor to develop minigames or workout routines.[33] Nowadays, there are some NRFA-published studies involving different pathologies and types of populations.[34–38] Nevertheless, as far as we are concerned, there is no evidence for the effectiveness of NRFA exergaming systems for physical therapy in PwMS. Moreover, none of the previous exergaming trials assessed the muscle strength and spasticity in lower limbs in PwMS. As a result, the present study protocol is needed to develop the first randomized controlled trial (RCT) including these relevant measurements and emerging interventions in PwMS.

Based on this background, the hypothesis proposed is that the exergaming systems in addition to conventional treatment will show statistically significant improvements in motor skills, spasticity, and quality of life results compared to conventional treatment alone.

Objectives

The main aim is to evaluate and compare the effectiveness of two specific exergaming systems in addition to conventional treatment on improving physical functional capacity, balance, muscle strength, spasticity in lower limbs, and quality of life in patients with multiple sclerosis. The secondary aim is to compare the effectiveness of each exergaming system to isolated conventional treatment.

Trial design

This is a study protocol for a multicenter, assessor-blind, 24-week RCT. This trial protocol was structured in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013 Statements).[39] Each item on the checklist has been allocated to a section of this protocol (Appendix A).

Methods

Participants and study setting

PwMS with routine conventional treatment at the Cordoba Multiple Sclerosis Association Center (MSAC) (Cordoba, Spain) and the Cadiz MSAC (Jerez de la Frontera, Spain) will be recruited. Both centers provide a 12-h/day ambulatory rehabilitation through a multidisciplinary specific service to a large number of PwMS.

The physical therapist coordinator of each MSAC will support the general information and provide participants with the details and purpose of the study to obtain their informed consent. The principal investigator will be responsible for contacting them to assess their interest in participating in the trial.

Eligibility criteria

The physical therapist coordinator of each MSAC will verify the eligibility criteria.

Inclusion criteria. The following inclusion criteria will be used: (i) diagnosis of any MS disease forms based on the McDonald criteria;[12] (ii) age over 18 years; (iii) Mini-Mental State Examination score > 19 points,[40] and (iv) Expanded Disability Status Scale score < 7.0.[20]

Exclusion criteria. The following exclusion criteria will be considered: (i) diagnosis of another disease with balance or coordination disorders; (ii) exacerbation or steroid treatment 30 days before the beginning of the trial; and (iii) visual disturbances.

Interventions

Participants will be allocated to three study groups: the control group (CG) will perform a conventional treatment of combined training whereas the experimental groups (EGs) will perform active videogame-based exercise programs in addition to the conventional treatment. A weekly follow-up will be performed (face-to-face, telephone call or WhatsApp message modalities) throughout the whole 24 weeks of the trial to supervise physical activity and ensure session attendance.

Control group. The CG will receive only conventional treatment for the entire 24 weeks of the study, based on daily routine activities and/or a single 45-min session/week of conventional physical therapy. It consists of a combined training based on the patient's program and objectives, including different modalities of exercise: aerobic training (walking, cycling, elliptical, treadmill, up and down stairs), resistance training (squats, lunges, hip bridges, single and multi-joint machines), and flexibility (global body stretching).[19]

Experimental groups. The EGs will perform a single 45-min session/week of exergame-based training for 12 weeks (weeks 1–12), in addition to the conventional treatment performed by the CG. Both EGs will undergo a treatment consisting of 3 phases: (i) warm-up for 5 min, (ii) specific exergame training comprising of total of 5 activities/session considering the variety of games and 1-min breaks between exercises. This phase varies according to the systems used (NRFA or NWF) in each experimental group, and it lasts 35 min, and (iii) cool-down for 5 min. The protocol is summarized in Table 1.

Table 1. Exergame training programs protocol.

Phase (Time)	Experimental Group 1 (Nintendo Ring Fit Adventure©)	Experimental Group 2 (Nintendo Wii Fit©)
Warm-up (5 min)	Joint mobility and global stretching	
Exergame training (35 min)	Jogging: 1 act/ses	Aerobics: 1 act/ses
	Minigames: 2 act/ses	Muscle strength training: 1 act/ses
	Lower limbs training: 1 act/ses	Balance games: 2 act/ses
	Yoga: 1 act /ses	Yoga: 1 act/ses
Cool-down (5 min)	Breathing exercises, joint mobility and global stretching	

Act/ses, Activities per session.

Experimental Group 1 (EG1) will use the NRFA system, a nonimmersive exergaming system in which the participants interact with virtual environments on the screen using the Nintendo Ring-Con© and Nintendo Joy-Con© sensors. The Nintendo Ring-Con© sensor can detect the force of players pushing or pulling on the ring controller, while the Nintendo Joy-Con© sensors use accelerometers and gyroscopes to detect a variety of movements such as spinning, tilting, stepping, or knee-bending.

The activities of this exergame training will be divided into four ordered sections: jogging, minigames, lower limbs training, and yoga. These sections are based on the NRFA system's own classification. Participants will complete one activity per section, except for the minigames section where participants will complete two activities. The different sections and activities are shown in Figure 1(A) and are detailed below:

1. Jogging: a normal speed race where you must overcome obstacles such as crates or mounds by jumping and pressing the Nintendo Ring-Con©. There are two courses: (i) Begginia (easy level); and (ii) Transient Temple (advanced level).
2. Minigames: short and playful activities suitable for most skill levels: (i) Squat Goals: the player must control the depth of the squat to jump at different heights collecting tokens and avoiding bombs; (ii) Squattery Wheel: the player must squat down to aim at the height of the robot's arms, then push in on the ring to make the arms enter and shape the clay, following the example; (iii) Gluting Gallery: the player holds the ring above the head and lean to avoid bombs and collect tokens; (iv) Bank Balance: a balance beam simulated by the ring to collect tokens and avoid bombs as you move forward; (v) Thigh Rider: sitting in a chair, the player press the ring between their thighs to collect tokens and earn points by jumping; and (vi) Dreadmill: the player must collect tokens and dodge bombs on a treadmill by jumping and blasting through the air by pressing the ring.
3. Lower limbs training: a more formal workout focusing on lower limb exercises with variable difficulty and repetition settings: (i) Knee Lift: the player must alternate between raising the knees and moving the arms with the ring up and forward for the set number of repetitions; and (ii) Hip Lift: the player must place the ring between their thighs, lie down with their knees bent and lift their hips for the set number of repetitions.
4. Yoga: strength, balance, awareness, and harmony in both the mind and body will be reached through the following poses: (i) Tree: a sustained single-leg position with the right foot pressed against the inner thigh of the left leg. The hands are extended upwards holding the ring. After performing a series of leaning repetitions on one side, the same procedure is repeated with the right leg on the other side; and (ii) Chair: in this position, sustained squat will be performed while the arms with the ring are raised to the front for the set of repetitions stablished.

Experimental Group 2 (EG2) will use the NWF system, another non-immersive exergaming system in which the interaction between the participant and the digital world is achieved via the Nintendo Wii Fit Balance Board©. This is a force platform equipped with four pressure sensors that measure the force applied to them and track shifts in the center of balance by monitoring changes in the center of pressure.

The activities of this exergame training will also be divided into four ordered sections: aerobics, muscle strength training, balance games, and yoga. These sections are based on the NWF system's own classification. Participants will complete one activity per section, except for the balance games section where participants will complete two activities. The different sections and activities are shown in Figure 1(B) and are detailed below:

1. Aerobics: activities that require vigorous movements: (i) Basic Run: the player runs in place while holding the connected Wii Remote in their pocket, which acts as a pseudo-pedometer; and (ii) Hula-Hoop: the player must get as many spins out of their hula hoop as possible in 70 s.
2. Muscle strength training: a series of exercises designed to improve muscular strength and endurance. The training will be focused on the lower limbs: (i) Rowing Squat: the player must squat down while performing a rowing motion; (ii) Single-Leg Extension: a single-leg stance position where the opposite leg is moved backward. After completing the set of repetitions, the same procedure will be repeated with the other leg; (iii) Sideways Leg Lift: a single-leg stance position where the opposite leg is raised and lowered sideways. The same procedure will be repeated with the other leg; and (iv) Single-Leg Twist: a single-leg stance position where the opposite leg is raised and lowered forwards. The same procedure will be repeated with the other leg.
3. Balance games: engaging and interactive activities that challenge the player's balance skills through stability and coordination training: (i) Ski Jump: the player must squat with their knees bent and push forward on the Nintendo Wii Fit Balance Board© to gain speed. At the end of the ramp, the player must extend their knees and then keep their balance for the landing; (ii) Balance Bubble: the player must guide the avatar safely down a river avoiding obstacles by leaning to the left, right, forward, and backward on the board; (iii) Table Tilt: the player must lean their body left, right, forward, and backward on the board to drop the balls into the holes; and (iv) Penguin Slide: the player must tilt their body left and right on the board to tip the iceberg and catch fish.

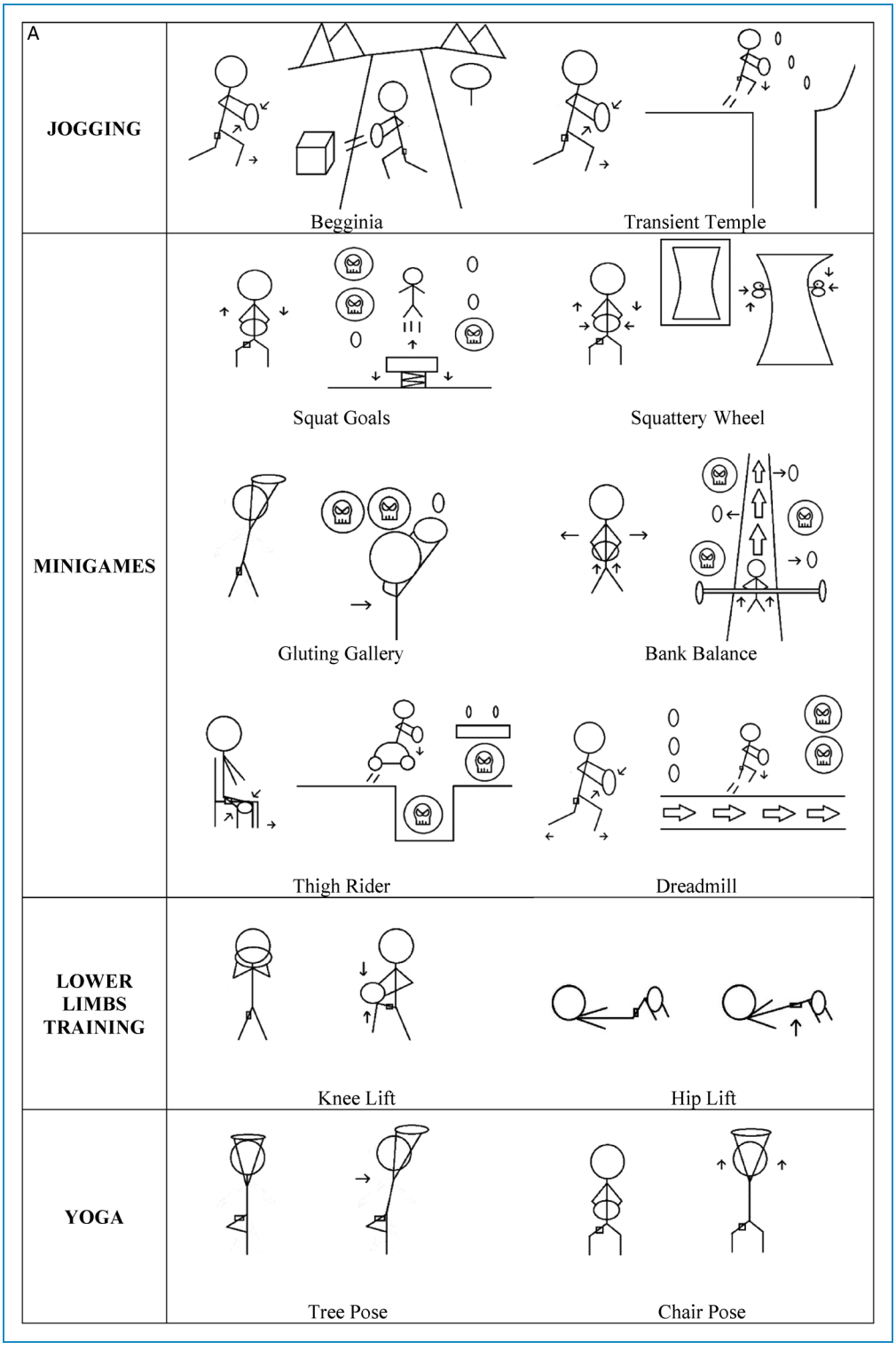

Figure 1. Physical activities for exergame training programs. (A) Experimental group 1 (Nintendo Ring Fit Adventure©); (B) experimental group 2 (Nintendo Wii Fit©). (continued)

4. Yoga: different poses used to increase physical flexibility, mental relaxation, and mindfulness through an enjoyable gaming experience: (i) Chair: the player must hold the position for 15 to 30 s (depending on the difficulty level) while bending the knees forward and lifting the heels on the board to adjust the center of gravity; and (ii) Standing Knee: a sustained single-leg position in which the knee of the standing

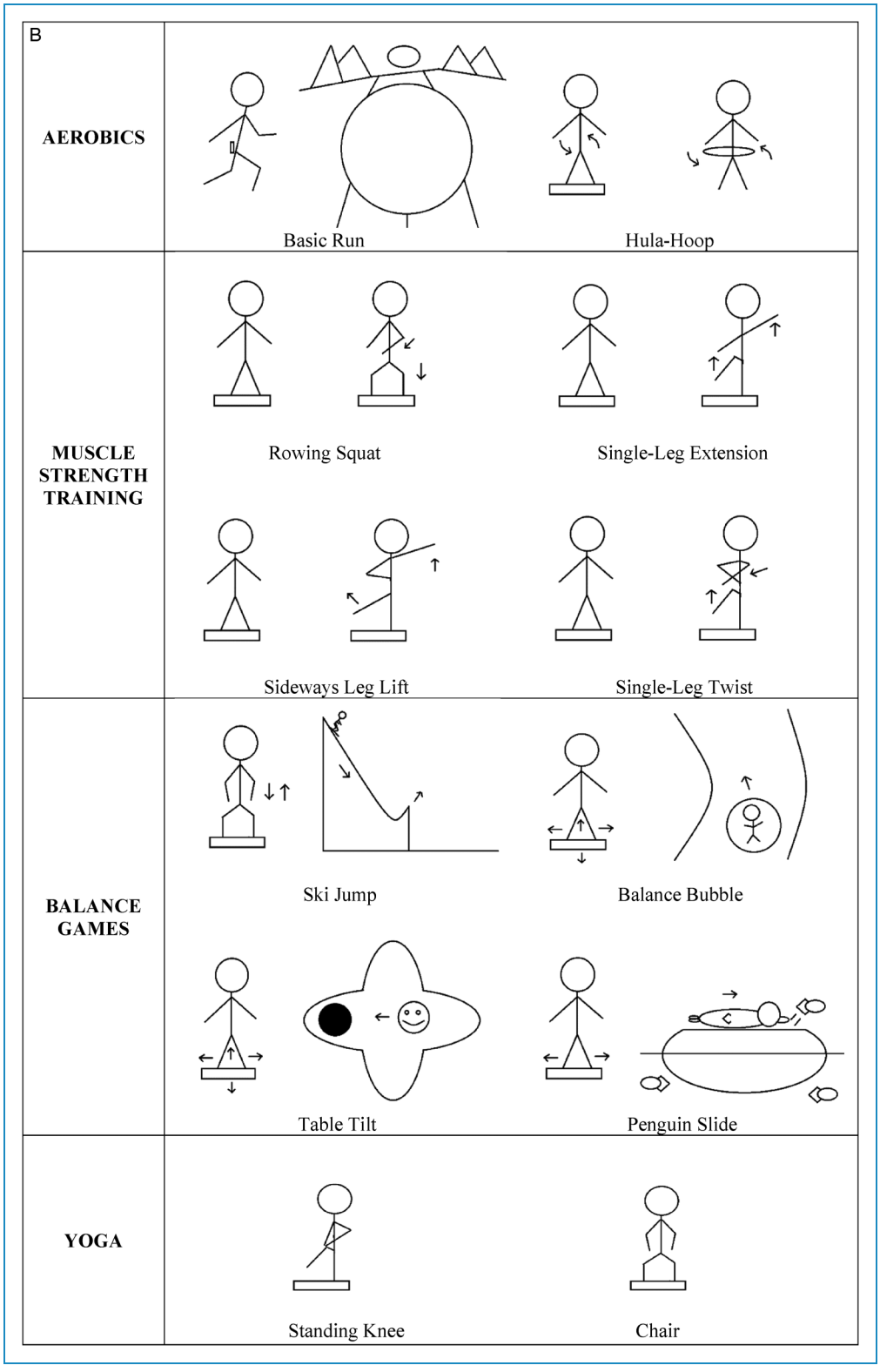

Figure 1. Continued.

leg is grasped with both hands, bringing them up to the abdomen. The center of gravity must be controlled while maintaining this position for 15 to 30 s (depending on the difficulty level). After this pose, the same procedure will be repeated with the other leg.

Given the physical limitations, multiple MS symptoms and varying levels of disability of participants, it will be essential to tailor these interventions to the needs of each patient to ensure the safety of the intervention. For this reason, before the start of the study, specialized training will be provided for the physical therapist coordinator by the principal investigator, considering the following cases: (i) mild cognitive impairments: the physical therapist will provide the instructions using easy-to-understand vocabulary combined with a quick demonstration at the start of each exercise. Movements and postures are guided at the first attempt. The support is gradually removed to ensure that the exercises are understood; (ii) severe balance and mobility disorders: large surface mats, parallel bars and handholds in rooms will prevent the risk of falls. In addition, if there is a possible disturbance in the base of support, the physical therapist will help to carry out static and dynamic balance exercises; and (iii) fatigue during the intervention: the breaks between the exercises will be increased in case of fatigue. In addition, if the participant is unable to complete an exercise due to fatigue, a higher level of support, a lower level of difficulty, or a reduction in the number of activities could be applied to complete the session.

A safe environment will be provided by conducting the intervention in a spacious room free of objects, and a physical therapist specialized in MS rehabilitation who will guide the progression of the games and monitor the accuracy of the participants' movements during the intervention, reducing the risk of falls or possible exacerbations as a result of incorrect movements. The temperature in the room will be between 20 and 25°C. There will also be 1-min breaks between activities. These will be used to check cardiorespiratory status with a pulse oximeter and to drink water. In the event of an emergency, both MSACs have medical staff and specific equipment to prevent and/or treat injuries or attacks during physical activities.

Outcomes

Sociodemographic characteristics (age, gender, type of MS, time since diagnosis, Expanded Disability Status Scale score, toxic habits, race, employment status, and lifestyle), anthropometric data (weight, height, and body mass index), and comorbidity information (mobility aid and medication) variables will be registered at baseline (t_0). The remaining outcomes will be assessed with their corresponding following measuring instruments at t_0 and at the 12 weeks (end of the exergame training programs, t_1) and 24 weeks (final follow-up, t_2) by the same blinded examiner of each MSAC at the same time and under the same state.

Physical functional capacity will be assessed by the 6-min walk test.[41] Heart rate, O_2, and effort perception (Borg Scale) data will also be collected. The intraclass correlation coefficient for PwMS was 0.96.[42]

Quality of life will be asked about using the Multiple Sclerosis Specific Quality of Life Questionnaire,[43] based on an SF-36 questionnaire[44] with 18 specific MS items added, that measures several quality-of-life dimensions. The Spanish version of questionnaire[45] will be used for this trial. The quality-of-life dimensions intraclass correlation coefficient ranged from 0.69 to 0.96.[43]

The Tinetti Balance Scale[46] will measure both static (12 points max) and dynamic balance (16 points max), thus enabling early detection of the risk of suffering a fall (high risk: <19 points, moderate risk: 19–23 points, low–mild risk: 24–28 points).[47] The Spanish version of the scale[48] will be used for this trial.

A handheld dynamometer will be used to evaluate the lower limbs' strength focusing on the maximum isometric voluntary muscle contraction.[49] The procedure and testing positions for muscle strength and power assessment of hip flexors, knee extensors, knee flexors, ankle plantarflexors, ankle dorsiflexors, hip abductors, hip adductors, and hip extensors will be based on Mentiplay et al.[50] The intraclass correlation coefficient with a knee dynamometer in PwMS was 0.97.[51]

Lower limb spasticity will be evaluated by the Modified Ashworth Scale,[52] a clinical tool used to assess muscle tone by measuring the level of resistance to passive movement. The procedure and testing positions for spasticity assessment of knee extensors, knee flexors, ankle plantarflexors, ankle dorsiflexors, hip abductors, and hip adductors will be based on Craven and Morris,[53] whereas hip flexor and extensor muscles will be determined by and Haas et al.[54]

Sample size

To achieve a power of 80.00%, considering a significance level of 0.05, using a repeated measures within-between interaction ANOVA test to detect differences between three intervention groups throughout three measurements over time, and assuming a size of the differences of 0.25, it will be necessary to include a total of 36 subjects according to GPower software.[55] Assuming a dropout rate of 10%, a final total sample size of 39 participants will be recruited by nonprobabilistic convenience sampling.

Assignment of interventions

Participants will be allocated to three groups of equal size. The CG will be composed of PwMS not interested in exergaming-based training. On the other hand, the EG will be randomly divided by the principal investigator according to the assignment of Epidat 3.1 software (Conselleria de Sanidade de la Xunta de Galicia, Santiago de Compostela, Spain). The program will generate two sets of 13 random numbers without repetition ranging from 1 to 26. According to the arrival order, EG participants will be divided into EG1 (NRFA) or EG2 (NWF). In the case of the sample size being exceeded, a balanced number of participants in both EGs will persist because

the probability of inclusion in each group will be inversely proportional to the number of participants already in that group.

Blinding

This study will be an assessor-blinded RCT. Baseline and post-intervention variables will be measured by the physical therapist coordinator of each MSAC, who will be unaware of participant allocation. The evaluation sessions will take place in different rooms and at different times from the intervention sessions.

Data collection

The collection of participant data and variables will be gathered as indicated in Figure 2.

Statistical methods

A descriptive statistical analysis of the data will be conducted using IBM SPSS v.29 software. The qualitative variables will be described by frequency distribution and the quantitative variables by mean and standard deviation. For the spasticity variable, the Modified Ashworth Scale values will be converted: (0 = 0; 1 = 1; 1+ = 2; 2 = 3; 3 = 4; 4 = 5). Shapiro–Wilk test will determine the normal distribution of quantitative variables. One-way ANOVA test will be used to evaluate the mean differences in baseline (t_0) variables between the intervention groups (CG, EG1, EG2) in case of normality, or Kruskal–Wallis test otherwise. The mean differences over time between and within groups will be compared using a mixed ANOVA test (with adjustments such as Pillai's Trace, Roy's Largest Root, Greenhouse-Geiser, or Lower Limit, if some assumptions such as normality or equality of variances fail) with time as the intra-group factor (t_0, t_1, t_2) and the intervention group as the inter-group variable (CG, EG1, EG2). If statistically significant differences are found, the Bonferroni post hoc test will be performed to identify specific differences between groups in case of normality, or the Games–Howell test otherwise. Although no significant data loss is anticipated, an intention-to-treat analysis will be conducted. In all cases, the significance level will be set to 0.05.

Ethics

The present clinical trial has been authorized by the Ethics Committee of Provincial Biomedical Research of Cordoba (Cordoba, Spain) and has been recorded in ClinicalTrials.gov (NCT06196866). The Consolidated Standards of Reporting Trials (CONSORT)[56] statement will be followed to disseminate the findings at Journal Citation Report publications, international conferences, and popular social networking platforms for scientists or academic institutions to reach a high research interest in this topic.

Confidentiality

The principal investigator will be responsible for preserving the participant data identity with a unique code (such as MS01) for each one. A password-protected computer in the case of electronic files or a locked closet for paper documents of each MSAC will maintain all data and project materials for a minimum of five years. After this period, electronic files will be deleted, and paper documents will be destroyed. The information will not be kept in cloud storage at any stage of the information transmission.

Discussion

This RCT aims to evaluate and compare the effectiveness of two different exergaming systems in addition to conventional treatment on improving physical functional capacity, balance, muscle strength, spasticity in lower limbs, and quality of life in PwMS. It is expected that the active videogame-based exercise programs in addition to conventional treatment will also demonstrate statistically significant improvements in motor skills, spasticity, and quality of life results compared to conventional treatment alone.

Playing serious games can be a viable option for use in many different genres and application areas (e.g., healthcare, education, research, computer science, or advertising),[57] and training specific motor skills using exergames has been shown to have promising potential for improving physical performance, especially in patients with motor impairments.[58] In fact, these results will align with previous exergaming research. In this context, to the best of our knowledge, there is currently no specific NWF or NRFA systematic review or meta-analysis available for PwMS. Nevertheless, the current literature has shown diverse NWF trials for PwMS. A study by Plow and Finlayson[59] showed NWF's potential benefits in increasing the physical activity of individuals with MS. With regard to balance, an RCT of NWF compared to a CG without intervention reported improvements,[30] although another two similar types of RCT intervention found no significant differences between groups.[31,32] This issue could be inconclusive because of the heterogeneity of participants' characteristics and the different frequency and duration of the interventions. Expanding on this perspective, another qualitative study stated that physical therapists must contemplate the patient environment, functional level, and preferences while prescribing individualized NWF-based exercise programs for PwMS.[60] Conversely, the preceding articles suggested significant evidence of improvements in functional capacity and independence,[29,30,32] as well as quality of life.[30] In view of no evidence of effectiveness on lower-limb muscle strength and spasticity in MS disease trials using

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	t_{-1}	0	t_0	t_1	t_2
ENROLMENT:					
Eligibility Screen	X				
Informed Consent	X				
Information Session	X				
Allocation		X			
INTERVENTIONS:					
Control Group (CG) Conventional Treatment			←	—	→
Exergaming Group 1 (EG1) Conventional Treatment + Nintendo Ring Fit Adventure©			←	—	→
			←	—	—
Exergaming Group 2 (EG2) Conventional Treatment + Nintendo Wii Fit©			←	—	→
			←	—	—
ASSESSMENTS:					
Baseline Variables Age, gender, MS type, time since diagnosis, EDSS score, toxic habits, race, employment status, lifestyle, weight, height, BMI, mobility aid, medication			X		
Physical Functional Capacity			X	X	X
Quality of Life			X	X	X
Balance			X	X	X
Lower Limbs Muscle Strength			X	X	X
Lower Limbs Spasticity			X	X	X

BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; MS, Multiple Sclerosis; t_{-1}, completed in clinical setting; 0, completed before first session; t_0, baseline assessment; t_1, end of the exergame training programs assessment (12 weeks); t_2, final follow-up assessment (24 weeks).

Figure 2. Time-schedule of enrolment, interventions, and assessments. Solid lines indicate periods of continuous or daily collection or assessment, whereas "X" indicates collection on specific days.

NWF, we can use as a reference a meta-analysis that reported overall inconclusive results in lower-limb muscle strength among older adults.[61] In this regard, another RCT of exergaming compared with an isolated traditional neurological physical therapy found no significant improvements in spasticity among patients with stroke.[62]

Due to the lack of systematic review or meta-analysis analyzing the effects of NRFA intervention in PwMS, the published literature will be compared to similar, though not specific, research. An RCT with healthy subjects reported that NRFA maintains or improves physical fitness when compared with a routine CG.[34] Another trial with chronic low back pain patients stated that NRFA is effective in reducing pain.[36] Additionally, elderly population trials found that NRFA is potentially effective in improving anticipatory balance and risk of falls,[35] muscle strength,[38] and functional independence for geriatric hospitalized patients.[37] Considering these results, exhaustive research is required to provide new knowledge about the NRFA intervention impact for treating people with neurological disorders. In fact, this is the first RCT researching the benefits of NRFA in PwMS as a starting point.

Finally, patient adherence could be enhanced by using exergaming in the prevention and rehabilitation of neurological diseases.[63] Current NWF intervention studies among patients with stroke reported a range of 70 to 99% adherence rate.[64] Accordingly, in this study the physical therapist coordinators and the principal investigator will be available for a weekly follow-up in order to control physical activity and ensure the session attendance. Moreover, each participant will have an avatar or virtual character profile to record daily exercise scores, assess their gaming preferences, and compare their own and other participants' progress over time. In consequence, this could mean an improvement in adherence, motivation, and healthy competition developing physical activity in a fun and safe environment.

Strengths and limitations of the study

The main strength of this study lies in the advantages of VR use for rehabilitation. Repetition, motivation, customization and feedback are differential elements of performing an individualized motor learning treatment with specific goals through a simulation of real-life scenarios.[65] Another strength is that dual-task activities will be included to enhance motor and cognitive abilities and consequently autonomy level,[66] regardless of the participant intervention group allocation. Moreover, an attractive therapeutic tool such as exergame-based training programs could facilitate functional independence in the daily routine. Furthermore, a home-based exergame training could be a viable alternative in the intervention of people with neurological disorders. In this regard, the current literature suggests the revision of care protocols for chronic stroke patients, including more rigorous, high-intensity therapy through telerehabilitation as an eligible option.[67] Nevertheless, the participant's background (socioeconomic status, home distractions, TV accessibility, responsibility, or social influence) should be considered.[60,68]

Some limitations of the proposed study need to be noted. We will be careful about these issues because session absences or trial dropouts could affect the interpretation of the results. As stated above, the heterogeneity of the MS participants' characteristics and symptoms could be a restricting factor to achieving full attendance to the sessions. Despite this heterogeneity, we will tailor the video game activities in terms of variety and difficulty (easy, medium, or advanced) according to the patient's clinical characteristics.[60] These exercises need to be carefully tailored, as very demanding tasks may be too challenging, leading to exacerbation of symptoms, or frustration due to lack of score improvement and/or overload/overexertion during performance. Another limiting consideration is the intensity of patients' exercise, as the once-weekly intervention frequency may not be sufficient to detect group differences in outcome measures for PwMS.[19] Even so, participants will receive self-control instructions and will be asked about usual activities in the weekly follow-up.

Conclusion

The suggested exergaming systems, sustained by a solid conceptual model, could have the potential to be a feasible and engaging additional therapeutic resource. This study follows the current scientific evidence recommendations for prescribing endurance and/or resistance exergame-based training programs for PwMS. The physical activities are easy to practice, allowing the free movement of the whole body, although supervised sessions are required to lead a better-quality treatment. As a result, we expect that this protocol of a low-risk RCT will be considered a promising initiative for incorporating exergames in clinical settings.

Abbreviations

CG	Control Group
EG	Experimental Groups
EG1	Experimental Group 1 (Nintendo Ring Fit Adventure©)
EG2	Experimental Group 2 (Nintendo Wii Fit©)
MS	Multiple Sclerosis
MSAC	Multiple Sclerosis Association Center
NRFA	Nintendo Ring Fit Adventure©
NWF	Nintendo Wii Fit©
PwMS	People with Multiple Sclerosis
RCT	Randomized Controlled Trial
VR	Virtual Reality

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Appendix A. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Section/item	Item no.	Description	Assessed on section/ subsection
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, Ethics and Ethical approval
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	Title page
Funding	4	Sources and types of financial, material, and other support	Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page and Contributorship
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

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Section/item	Item no.	Description	Assessed on section/ subsection
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction
	6b	Explanation for choice of comparators	Introduction
Objectives	7	Specific objectives or hypotheses	Objectives
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Trial design
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Participants and the Study setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Eligibility criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Interventions, Table 1 and Figure 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Exclusion criteria
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Exclusion criteria
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Outcomes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

(continued)

Continued.

Section/item	Item no.	Description	Assessed on section/ subsection
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample size
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
Methods: Assignment of interventions (for controlled trials			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	Assignment of interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Assignment of interventions
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Participants and the Study setting and Assignment of interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Outcomes
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Outcomes and statistical methods

(continued)

Continued.

Section/item	Item no.	Description	Assessed on section/ subsection
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Confidentiality
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Statistical methods
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Statistical methods
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Statistical methods
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Contributorship
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Statistical methods
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	Participants and the Study setting
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-

(continued)

Continued.

Section/item	Item no.	Description	Assessed on section/ subsection
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Confidentiality
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Conflicting interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Confidentiality
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Confidentiality
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Ethics and Confidentiality
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.