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Effects of exergames training on Postural Balance in chronic stroke patients: study protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038593
Article Type:	Protocol
Date Submitted by the Author:	16-Mar-2020
Complete List of Authors:	Bessa, Nathalia; UFRN, Lima Filho, Bartolomeu; Federal University of Rio Grande do Norte, Department of Physical Therapy Medeiros, Candice; Federal University of Rio Grande do Norte, Department of Physical Therapy Ribeiro, Tatiana; Federal University of Rio Grande do Norte, Department of Physical Therapy; Federal University of Rio Grande do Norte Campos, Tânia; Federal University of Rio Grande do Norte, Department of Physical Therapy Cavalcanti, Fabrícia; Federal University of Rio Grande do Norte, Department of Physical Therapy
Keywords:	Stroke < NEUROLOGY, REHABILITATION MEDICINE, Neurology < INTERNAL MEDICINE

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1 **Effects of exergames training on Postural Balance in chronic**
2 **stroke patients: study protocol for a randomized controlled trial**

3
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16 **Date:** 11 March 2020

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18 **Version:** 1

19
20 **Word Count:** 3994

1
2
3 **Abstract**
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5
6 **Introduction:** Exergames training, as an additional therapy to standard care,
7
8 has been widely used for motor recovery after stroke. However, there is
9
10 insufficient evidence to reach conclusions about the isolated effectiveness of
11
12 exergames on gait speed, balance, and the quality of life compared to that of
13
14 traditional rehabilitation training. The study describes a single-blind randomized
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16 clinical trial that aim is to investigate the effects of exergames training on
17
18 postural balance in patients with chronic stroke.
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21
22 **Methods and analysis:** Forty-two individuals with chronic stroke (> 6 months),
23
24 aged from 20 to 75 years, will be randomized into two groups: experimental
25
26 group, which will be submitted to an exergames protocol and control group
27
28 which will undergo kinesiotherapy protocol, both protocols are based on
29
30 postural balance. The intervention will consist of 40-minute sessions twice a
31
32 week for 10 consecutive weeks. The volunteers will be evaluated before the
33
34 treatment, at the end of the interventions and 8 weeks after. The primary
35
36 outcome will be postural balance, and secondary outcomes will be gait, cortical
37
38 activation patterns, functional independence, quality of life, and motivation.
39

40
41 **Ethics and dissemination:** This protocol has been approved by the Ethics
42
43 Committee of Federal University of Rio Grande do Norte (number: 3.434.350).
44
45 The results of the study will be disseminated to participants through social
46
47 networks and will be submitted to a peer-reviewed journal and scientific
48
49 meetings.
50
51

52
53 **Trial registration number :** RBR-78v9hx (Brazilian Registry of Clinical Trials –
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55 ReBEC).
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Keywords: Stroke, Randomised Controlled Trial, Postural balance, Rehabilitation, Physical therapy modalities, Virtual Reality Exposure Therapy.

Strengths and limitations of this study

- This study will be explore objective data of the postural balance and gait through the force platform and kinematic analysis;
- This study is among the few that use EEG to assess brain activity in stroke individuals undergoing in an experimental protocol with exergames;
- The results of this research can lead to enhancements about how to improve the use of exergames for postural balance in the stroke rehabilitation;
- This study should benefit participants not only in physical aspects but also in psychological and social aspects;
- The blinding of participants will be not possible because the nature of the intervention;

63 Introduction

64 According to the World Health Organization, cerebrovascular disease
65 was the leading cause of death worldwide in 2016. Of those deaths, 5.78 million
66 were directly attributed to stroke, making it the main non-communicable cause
67 of death¹. In Brazil, stroke resulted in approximate 100,000 deaths in 2014², and
68 data indicate that about 568,000 affected individuals suffer from severe
69 disability, making stroke the leading cause of disability in adults³.

70 Following stroke, various aspects of balance function are altered, such as
71 delay in regaining the ability to assume the standing posture, loss of balance,
72 asymmetry between the right and left limbs, increased posture sway, and
73 decreased weight bearing on the affected side^{4,5}. Postural balance is important
74 for functional tasks such as sitting, sit-to-stand, and walking, and dysfunction
75 leads to alterations in weight distribution patterns, causing the paretic leg to
76 take less load⁶. These changes promote high risk of falling, difficulties in
77 executing functional activities and reduced performance of daily living activities,
78 and a consequent reduction in social participation which can aggravate the
79 clinical situation⁷.

80 Underuse of the impaired limb results in suppression of the cortical
81 representation of the affected limb and further inhibition of its use⁸. The
82 existence of cortical neural resources specialized in capturing changes in
83 postural stability, which have been detected by changes in
84 electroencephalography (EEG), support the idea that postural adjustments are
85 not only due to muscle responses to disorders but also due to cortically
86 controlled intentional movements that may be altered following stroke⁹.

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2
3 87 One major component of stroke rehabilitation is exercise therapy¹⁰ and
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5 88 motor skill learning is particularly attractive since practice-induced improvement
6
7
8 89 of sensorimotor performance supports the development of new aptitudes,
9
10 90 providing the flexibility to adapt to changing conditions¹¹.

11
12 91 These perspective, virtual reality (VR)-based exercises, also known as
13
14 92 exergames, have been widely used in rehabilitation with the aim of improving
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17 93 sensorial, cognitive, psychological, and motor function^{12,13}. They have been
18
19 94 characterized as an experience that simulates a real environment in which the
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21
22 95 user can interact with the scenario created by the game through the
23
24 96 involvement of multisensory aspects¹⁴. Exergames applications have the
25
26 97 potential to apply relevant concepts of neuroplasticity, such as repetition,
27
28 98 intensity, and task-oriented training of the paretic extremity⁷, and may entrain
29
30
31 99 several brain areas involved in motor planning and learning, thus leading to an
32
33 100 enhanced motor performance in rehabilitation^{12,15,16}.

34
35 101 There is some evidence to suggest the effectiveness of exergames in
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37 102 improving upper limb function and balance as an additional therapy to standard
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40 103 care in stroke patients. However, there is insufficient evidence to reach
41
42 104 conclusions about the isolated effectiveness of exergames on gait speed,
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44 105 balance, participation, or the quality of life compared to that of traditional
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46 106 rehabilitation training^{17,18}.

47
48
49 107 A meta-analysis by Lee *et al.* (2019) found moderate evidence to support
50
51 108 the effect of exergames training on improved lower limb function, including
52
53 109 balance and gait, to a similar degree as upper limb function in chronic stroke
54
55 110 patients, suggesting that this technique may be used as a complementary
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58 111 treatment method alongside traditional rehabilitation therapy. However, most of
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3 112 the studies in this meta-analysis increased the overall treatment time by adding
4
5 113 exergames training to conventional treatment, and this may be the reason for
6
7
8 114 the observed outcomes¹⁹.

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10 115 Considering the above evidence, it is paramount to investigate the
11
12 116 isolated effectiveness of exergames rehabilitation and its contributions to
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14 117 positive changes in postural balance in stroke patients as this may provide
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17 118 additional evidence for the rehabilitation process in this population. The
18
19 119 proposal of the study is to investigate the effects of exergames training on
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21 120 postural balance in patients with chronic stroke and to explore changes in
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23
24 121 cortical activation patterns, functionality, quality of life, and motivation.
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26 122

27 28 123 **Methods and Analysis**

29 30 31 124 **Design**

32
33 125 A single-blind randomized controlled clinical trial that follows the
34
35 126 recommendations of the Standard Protocol Items: Recommendations for
36
37 127 Interventional Trials (SPIRIT)²⁰ (Figure 1) . Participants will be randomised to
38
39 128 receive exergames protocol (experimental group - EG) and kinesiotherapy
40
41 129 protocol (control group - CG) (Figure 2).

42
43
44
45 130 [INSERT Image 1]

46 131 [INSERT Image 2]

47 132

48 49 133 **Participants**

50
51 134 The study population will consist of forty-two chronic stroke patients who
52
53 135 live in the city of Natal or nearby. A volunteer selection will be carried out in
54
55 136 stroke patient care centers in the city. The selection can also be carried out via
56
57
58 137 spontaneous demand by the voluntary search of stroke patients after project
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3 138 advertisement on social media. After this, the first telephone contact will be
4
5 139 made to clarify any questions from the participants, and the first screening for
6
7 140 inclusion will be performed.
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12 142 **Inclusion and exclusion criteria**

14 143 The participants will be selected according to the following criteria: (1)
16 144 first episode of unilateral stroke (ischemic or hemorrhagic); (2) postural balance
18 145 deficits (Berg Balance Scale score -BBS) <45 ²¹; (3) injury time ≥ 6 months; (4)
20 146 age between 20 and 75 years; (5) at maximum level 2 of the modified Ashworth
22 147 Scale to assess the spasticity of the paretic lower limb²²; (6) good cognitive
24 148 status based on the Mini-Mental State Examination (MMSE)²³; (7) ability to walk
26 149 without personal assistance indoors (Functional Ambulation Category -FAC)
28 150 scores ≥ 3 ²⁴; (8) clinically stable, with no history of epilepsy or seizures in the
30 151 last 6 months; (9) not having signs of unilateral neglect or sensory or global
32 152 aphasia as assessed by National Institute Health Stroke Scale -NIHSS²⁵; (10)
34 153 no uncorrected hearing and/or visual impairments; (11) not participating in a
36 154 balance treatment protocol; and (12) ability to understand and obey simple
38 155 motor commands.
40
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44 156 Exclusion criteria will include (1) presenting other clinical conditions
46 157 affecting balance and (2) pregnancy.
48

49 158

51 159 **Sample Size**

53 160 Using an online calculator²⁶ and based on previous study values
55 161 (51.0 ± 4.6 and 46.2 ± 5.7)²⁷ a total sample of participants 42 (21 in EG and 21 in
57 162 CG) will be sufficient to detect a clinically important difference between the
59
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1
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3 163 groups on the BBS. A statistical power of 80% and an alpha of 5% and a loss
4
5 164 rate of 10% were considered for the sample calculation.
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10 166 **Randomization and blinding**
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12
13 167 A randomization sequence will be generated by a computer²⁸ in 3 blocks
14
15 168 of 12 participants and 1 block of 6 participants, allowing participants to be
16
17 169 equally distributed between the 2 groups. This stage will be conducted by a
18
19 170 researcher, not involved in the study, which will keep the randomization list
20
21 171 confidential until the end of the study and will organize the allocation in
22
23 172 sequentially numbered opaque envelopes. These envelopes will be sealed, and
24
25 173 the randomization sequence will be enforced using color coding for the study
26
27 174 groups (blue and red) that will correspond to the protocol that will be executed.
28
29 175 The contents of each envelope will be revealed at the beginning of each
30
31 176 patient's training by the study therapists responsible for the intervention to
32
33 177 maintain allocation confidentiality. The same therapists involved in CG training
34
35 178 will perform training in the EG. The researcher responsible for evaluations will
36
37 179 be blinded to all intervention groups. The only variables that will be collected
38
39 180 during the training will be evaluated by study therapists (non-blind). Statistical
40
41 181 analysis will be performed by a blind researcher who will treat the groups
42
43 182 according to color and the equivalence between groups and colors will be
44
45 183 revealed upon completion of the statistical analysis. The main researcher
46
47 184 (assessment) will have access to the final trial dataset; this researcher will
48
49 185 decide terminate the trial. All information about participants will be confidentiality
50
51 186 before, during and after the trial.
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188 **Evaluation procedures**

189 The researchers will be trained before data collection procedures to
190 ensure the reliability of measurements and the participants will be submitted to
191 assessment using all the instruments mentioned bellow.

193 **Measures**

194 **Sample characterization measures**

- 195 • Cognition: MMSE is a validated instrument in Brazil to assess cognitive
196 function. The total score ranges from 0 to 30 points, and the higher the
197 score, the better the cognitive ability, according to education. Good
198 cognitive status is considered with scores equal to or higher than 24
199 points for literate persons and 19 for illiterate persons²³.
- 200 • Ability to walk: This will be evaluated by the FAC which is a sensitive and
201 reliable instrument for gait evaluation in stroke patients with
202 hemiparesis²⁴ and ranks the ability to walk according to the amount of
203 physical support required for the task. The score can vary from 0 (unable
204 to walk or needs the help of 2 therapists) to 5 (independent in
205 locomotion).
- 206 • Spasticity: The modified Ashworth scale allows subjective assessment of
207 muscle tone and classifies the affected segments from 0 (normal tone) to
208 5 (rigid affected part)²².
- 209 • Clinical and demographic data: Personal information, anthropometric
210 data, demographic partner and pathological (injury time, paretic side,
211 stroke type) and clinical history (history of falls, physical therapy
212 treatment, and previous use of exergames) will be collected.

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3 213 • Neurological impairment: NIHSS is a specific instrument to assess the
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5 214 severity of stroke via 10 items and is reported to have excellent validity
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7 215 and reliability²⁵.
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12 217 **Outcome measures**

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15 218 Primary outcome measures considered for this study are as follows:

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17 219 **Postural Balance:**

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19 220 • Berg Balance Scale: BBS is a valid and reliable instrument for measuring
20
21 221 both the static and dynamic aspects of balance in people after stroke.
22
23 222 BBS scores range from 0 to 56, and values below 45 points are
24
25 223 predictive of falls, indicating a significant change in balance^{21,29}. In the
26
27 224 present study, test scores with the paretic limb positioned behind will be
28
29 225 used in item 13 and unipodal support over the paretic limb will be used in
30
31 226 item 14, minimizing the ceiling effect in individuals with better balance³⁰.
32
33 227 • Functional Reach Test (FRT): FRT assesses a patient's stability by
34
35 228 measuring the maximum distance an individual can reach forward while
36
37 229 standing in a fixed position, as is widely used to identify the risk of
38
39 230 falling³¹. Displacements < 15 cm indicate patient fragility and risk of
40
41 231 falls³².
42
43 232 • Timed up and Go test (TUG): It is a valid instrument for assessing
44
45 233 mobility and functional balance involving power, speed, and agility³³.
46
47 234 Performing the test within 10 seconds is considered normal for healthy,
48
49 235 independent adults without the risk of falls. Values from 11 to 20 seconds
50
51 236 are expected for disabled or frail elderly people with partial independence
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237 and a low risk of falls. Values > 20 seconds suggests that the elderly
238 have significant physical mobility deficits and risk of falls³⁴.

239 • Centre of Pressure variables (CoP): Data for total displacement,
240 anteroposterior, and midlateral velocity of the CoP will be assessed using
241 the gold standard equipment for balance assessment, the force platform
242 (FP)³⁵. The Bertec® model 4060 connected to an external amplifier
243 (Bertec® AM651X) will be used.

245 The following secondary outcome measures are considered for this study:

247 **Cortical Activation Pattern**

248 Alpha and beta frequencies will be evaluated due to their relationship
249 with the motor learning process³⁶, using the Emotiv EPOC®, portable 14 sensor
250 electroencephalography (EEG) device, gyroscope capable of detecting changes
251 in the movement performed.

253 **Gait kinematic analysis**

254 The spatiotemporal and angular gait variables will be evaluated by the 6-m
255 timed walk test and Kinovea® software.

256 • Six-Meter Timed Walk (6MTW): It is a valid and reliable test for the
257 assessment of the walking ability of patients with stroke³⁷. Gait speed
258 should be self-selected and considered comfortable and usual for the
259 participant. Studies show variation in mean habitual speed (0.45 m/s -
260 0.78 m/s) of gait in individuals with hemiparesis^{38,39}.

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3 261 • Software Kinovea®: Kinematic evaluation will be performed during gait
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5 262 video capture (6MTW) using the Sony DCR-DVD850 digital cam, 2.7/6.7
6
7 263 cm LCD screen, 60x optical zoom. Data will later be exported to
8
9 264 Kinovea® 0.8.15 software for paretic lower limb angle and gait speed
10
11 265 analysis. This is public domain video editing and analysis software that is
12
13 266 valid, reliable, and capable of accurately measuring distances up to 5
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15 267 meters from the object⁴⁰.
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21 269 **Functional independence**

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24 270 The Functional Independence Measure (FIM) scale will be used due to
25
26 271 its reliability, validity, precision, and feasibility criteria. It is composed of 18 items
27
28 272 including motor and cognitive items, in a system where the patient's answers
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30 273 graduates from 1 (total dependent) to 7 (complete independence) and the total
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32 274 punctuation ranges between 18 and 126. For this research, the FIM will be
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34 275 applied exclusively to the motor items, limiting the minimum score to 13 and the
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36 276 maximum to 91 points⁴¹.
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42 278 **Quality of life**

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44 279 The assessment of quality-of-life perception will be performed through a
45
46 280 quality-of-life assessment scale in stroke (Stroke-Specific Quality of Life Scale
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48 281 [SS-QoL]). It is valid and reliable in assessing the quality of life after stroke in
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50 282 the Brazilian population and has 49 items distributed over 12 domains⁴².
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56 284 **Motivation**

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3 285 Intrinsic Motivation Inventory (IMI) is a multidimensional measurement
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5 286 with 6 subscales used to assess the subjective experiences of participants
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7 287 when developing an activity and attends to the reliability, validity criteria.
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10 288 According to the inventory, instruction participants ranked their agreement with
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12 289 each statement on a Likert scale of 1 (“not at all true”) to 7 (“very true”)⁴³.
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17 291 **Participant monitoring measures**

19 292 Participants will be monitored during interventions by the following measures:

- 21 293 • Cardiovascular parameter variables: Heart rate (HR) will be checked by
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23 294 portable oximeter and Blood pressure (BP) by sphygmomanometer
24
25 295 (Visomat Comfort III®, Incoterm, São Paulo, Brazil) on the non-paretic arm.
- 26 296 • Adverse symptoms, perceived effort, and pain: Information regarding
27
28 297 headache, vomiting, and dizziness will be collected. Quantification of
29
30 298 perceived effort and pain will be used as indicators to monitor exercise
31
32 299 tolerance through the CR-10 (Category-Ratio Scale) Borg Scale⁴⁴ modified
33
34 300 by Foster *et al.*⁴⁵ (2001).
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42 302 **Adverse events**

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44 303 Additional information such as hospitalizations, falls, out-of-routine
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46 304 medical consultation, medication change, new diagnosis, and presence of
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48 305 negative event will be collected during the follow-up.
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54 307 **Interventions**

55
56 308 The protocols in both groups will be performed individually through 40-
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58 309 minute sessions twice a week for 10 weeks (total of 20 sessions), totaling 13
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hours of intervention^{12,17,46}. The same outcome measures and motivation will be collected again at the end of the interventions (post-training) and after 8 weeks of the end of the interventions (follow-up). All participants will be instructed not to perform any other physical activity that works on body balance during the study period.

During each session, the absences, manifestations of adverse symptoms, and occurrence of imbalance and/or falls will be recorded. Interventions modifications will be performed according patient's level of adaptation involving optimization of time or number of repetitions; and/or rest time enlargement and all will be registered.

Both groups will begin their protocols with adapted lower limb strength training for 10 minutes^{47,48} as described in Table 1. Each exercise should be performed with respect to the patient's level of adaptation and evolution will occur in the 6th and 13th sessions using the materials described.

Table 1. Lower limb strengthening exercises.

Exercise	Evolution	Materials Used	Sets
1. Get up and sit on a chair	Surface change	1 or 2 mats to create an unstable surface (H: 3 x W: 43 x L: 93 cm).	2 sets of 60 seconds with 30 seconds of rest
2. Go up and down steps	Increase the step height; add weight	Larger step and 1 kg shin pad.	
3. Strengthening of hip extensors	Add weight	1 kg and 2 kg shin pad.	
4. Tiptoe rise	Add weight	1 kg and 2 kg shin pad.	

Source: adapted from Allet et al. (2010).

Control Group

329 Participants in the CG will receive a kinesiotherapy protocol (30 minutes)
 330 (Table 2) focusing on balance based on previous studies and promotes stimuli
 331 similar to the EG and were selected so that they demand identical motor
 332 sensors in both intervention environments, real and virtual⁴⁷⁻⁵⁰. Two
 333 progressions will happen, respectively, in the 6th and 13th sessions.

334
 335 **Table 2.** Kinesiotherapeutic protocol exercises.

Exercise	Evolution	Materials Used	Sets**
1. Gait training on a stable surface.	Gait training on an unstable surface using mats; addition of shin pads of 1 kg.	Mat* and 1 kg shin pads.	2 sets of 3 minutes
2. Laterolateral weight transfer and discharge.	Addition of 1 and 2 mats respectively.	Mat	3 sets of 60 seconds
3. Anteroposterior weight transfer and discharge.	Addition of 1 and 2 mats respectively.	Mat	3 sets of 60 seconds
4. Laterolateral cephalic movement with eyes open.	Same movement with eyes closed. Added an exercise mat.	Mat	3 sets of 60 seconds
5. Anteroposterior cephalic movement with eyes open.	Same movement with eyes closed. Added an exercise mat.	Mat	3 sets of 60 seconds
6. Dissociation of scapular and pelvic girdles.	Addition of 1 and 2 mats respectively.	Mat	3 sets of 2 minutes

336 Source: Adapted from Nascimento, Patrizzi, Oliveira (2012); Soares, Sachelli (2008);
 337 Allet et al. (2010) e Ribeiro (2015). Legend: *The mats (height: 3 x width: 43 x length:
 338 93 cm) will be used to create an unstable surface; **For each series performed, the
 339 participant will be entitled to 30 seconds of rest.

341 **Experimental Group**

342 Participants in the EG will receive a seven Wii Fit Plus exergames on the
 343 Nintendo Wii® (30 minutes) (Table 3). This will use the Wii Balance Board
 344 (WBB) accessory, a multimedia projector, the Wii Remote Controller and

345 initially, participants will have a moment to adapt to Nintendo Wii and its
346 components.

347

348 **Table 3.** Exergames protocol exercises.

Game	Description	Progression
1. Free Run	Control in patient's pocket "marching" on firm surface	Addition of 1 and 2 mats* respectively
2. Soccer Heading	On WBB; performs anteroposterior and laterolateral weight transfer to virtually "hit" the head on the ball, with an attempt of 180 s and a throw of 80 balls	Addition of 1 and 2 mats respectively
3. Pinguim Slide	On WBB; performs laterolateral weight transfer in order to "catch" the largest number of fish, with 3 attempts of 60 s	Addition of 1 and 2 mats respectively
4. Ski Slalom	On WBB; performs laterolateral weight transfer for the purpose of deflecting obstacles, and anteroposterior weight transfers to control speed while skiing on the mountain, with three 60-s attempts	Addition of 1 and 2 mats respectively
5. Table Tilt	On WBB; performs small laterolateral and anteroposterior displacements as a simulation of an unstable board to place the balls inside holes, with 3 attempts of initial 30 s. You gain 20 s every 1 level you reach so that you do not exceed 180 s	Addition of 1 and 2 mats respectively
6. Free Steps	Up and down WBB, alternating feet with eyes open for 180 s	Addition of weights of 1 kg and 2 kg, respectively
7. Balance Bubble	On WBB; performs laterolateral and anteroposterior body displacement without the bubble touching the banks of the virtual river for 180 s	Addition of 1 and 2 mats respectively

349 Legend: Each game will be executed for 3 minutes with a rest interval of approximately
350 1 minute; *The mats (height: 3 x width: 43 x length: 93 cm) will be used to create an
351 unstable surface.

352

353 The games were pre-established with a focus on balance and demands

354 similar to that of the kinesiotherapy protocol: saccadic stimulation,

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3 355 visuovestibular cephalic movement, proprioceptive stimulus, dynamic balance
4
5 356 training, static gait, ankle and hip strategies, fine CoP control, stimulus
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7 357 optokinetic, double task (motor), and motor coordination⁵¹⁻⁵³; and all scores
8
9 358 obtained in games will be noted. The progressions will happen upon adaptation
10
11 359 of the patient, recommending 2 evolutions, respectively, in the 6th and 13th
12
13 360 sessions.
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19 362 **Adherence**

21 363 Participants will be contacted by telephone to confirm assessment and
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23 364 training sessions to avoid sample loss. Replacement of faults and performed
24
25 365 interventions by engaged and motivated professional will be performed to
26
27 366 increase adherence. Regardless of the protocol, the criteria for non-adherence
28
29 367 will be considered as follows: (1) absence > 30% of the intervention,
30
31 368 consecutively and without replacement; (2) presenting persistent pain or severe
32
33 369 discomfort (headache, vomiting, dizziness, etc.), which prevents continuity in
34
35 370 performing the proposed protocol in future sessions (or both); (3) presenting
36
37 371 hemodynamic instability: descompensation of systemic arterial pressure
38
39 372 (systolic and diastolic values > 200 mmHg and 110 mmHg, respectively)⁵⁴ and
40
41 373 HR above the submaximal values allowed during the training maintained even
42
43 374 after pauses, calculated by means of the formula $[HR_{sub} = 0.75 \times (220 -$
44
45 375 $age)]^{55}$; (3) those who do not adapt to the proposed intervention.
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53 377 **Data acquisition**

55 378 For data collection of the CoP variables, 6 static balance tests will be
56
57 379 performed on the FP based on their complexity variation and common use in
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3 380 the literature^{56,57}: bipodal support on a stable surface with eyes open and eyes
4
5 381 closed for 30 s each; unipodal support of paretic limbs on a stable surface with
6
7 382 eyes open and eyes closed for 30 s each; unipodal support of non-paretic limb
8
9 383 on a stable surface with eyes open and eyes closed for 10 s each. The distance
10
11 384 between the patients' feet will be standardized⁵¹ and in unipodal support tasks,
12
13 385 the contralateral knee may be slightly flexed and there may be no contact
14
15 386 between the raised and support leg. Each test can have 1 successful attempt
16
17 387 and a maximum of 3 unsuccessful attempts. The attempt is considered invalid if
18
19 388 the participant moves their support leg or touches the floor with the contralateral
20
21 389 leg⁵⁸.

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25
26 390 For gait analysis during 6MTW, the camera will be positioned
27
28 391 perpendicular to the plane of motion, at a height of 1 m and 3 m away from the
29
30 392 subject to capture gait pattern of the hemiparetic side, and will be considered as
31
32 393 complete gait cycle. Markers will be placed on the main bone references of the
33
34 394 paretic lower limb (greater trochanter of the femur, lateral tibial condyle, lateral
35
36 395 fibular malleolus, fifth metatarsal head, and lateral calcaneal bone tuberosity)
37
38 396 for further analysis.

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41
42 397 For encephalographic recording during the FP static balance and walking
43
44 398 tests, the Emotiv Epoc headset will be positioned on the user's head according
45
46 399 to the international placement in 10-20 positioning system following the
47
48 400 manufacturer's specifications⁵⁹.

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402 **Data processing**

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54 403 The Bertec® Model 4060 platform will be synchronized with Qualisys
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56 404 Motion Capture Systems (Qualisys Medical AB, 411 13 Gothenburg, Sweden),
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3 405 and through that system software, Qualisys Track Manager, data for CoP will be
4
5 406 collected and converted to MATLAB compatible files (the Mathworks, Natick, RI,
6
7 407 USA). The sampling rate will be 40 Hz, and a Butterworth bandpass filter with a
8
9 408 cutoff frequency of 15 Hz will be applied to eliminate noise contamination.

10
11
12 409 For kinematic analysis, the videos will be converted to an Audio Video
13
14 410 Interleave (AVI) file extension and exported to Kinovea software. Hip, knee, and
15
16 411 dorsiflexion flexion angles will be evaluated in the middle oscillatory phase of
17
18 412 gait, using as reference the follows joints: hip, tibiofemoral
19
20 413 metatarsophalangeal and calcaneal. Emotiv EPOC data processing will follow
21
22 414 the model used by Oliveira *et al.*⁶⁰ (2018). The encephalographic recording will
23
24 415 take place during gait and static balance tests, using 10 s of single-leg support
25
26 416 activity and a central 10-s cut-out in bipodal support activities.

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32 33 418 **Statistical analysis**

34
35 419 The SPSS (Statistical Package Social Science) V.21.0 software program
36
37 420 will be used and significance level of 5% and CI of 95% will be implemented for
38
39 421 all statistical analyses. Descriptive analysis of the sample characterization
40
41 422 variables will be performed through central tendency and dispersion measures.

42
43 423 The Kolmogorov-Smirnov test will initially be performed to evaluate the
44
45 424 normality of the data. To intragroup comparisons t-Student test or Wilcoxon test
46
47 425 will be used. Intergroup comparisons will be evaluated using ANOVA or
48
49 426 Kruskal-Wallis, depending on the normality of the data. Intention-to-treat
50
51 427 analysis will be performed for dropout data, considering the last data obtained
52
53 428 from the participant.

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430 **Patient and public involvement**

431 Patients were not involved in the design of this trial, establishing the
432 research question or developing recruitment procedures. At the end of the
433 study, the results will be reported to the participants in the form of a lecture,
434 showing the effects found in the studied variables. The results of the study will
435 be disseminated to participants through social networks and will be submitted to
436 a peer-reviewed journal and scientific meetings.

438 **Ethics and dissemination**

439 This research was approved by the Research Ethics Committee of the
440 Federal University of Rio Grande do Norte, with protocol number 3.434.350 in
441 July 3, 2019 and trial registration number RBR-78v9hx (Brazilian Registry of
442 Clinical Trials). Participants will be informed of the study objectives, its risks and
443 benefits, and when eligible for inclusion, if they agree to participate, must sign
444 the informed consent before the study begins. They will be free to abandon the
445 study at any time without the obligation of giving any explanation.

446 There will be prior contact with individuals through social networks, when
447 all information about the study will be presented, as well as the Resolution No.
448 466/2012 of the Brazilian National Health Council of 2012, which provides
449 guidelines and standards for research involving human subjects. In case any
450 negative effects occur, participants who suffer harm from trial participation will
451 receive physical assistance according to the injury. The study results will be
452 disseminated to participants through social networks and will be submitted to a
453 peer-reviewed journal and scientific meetings.

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3 455 **Protocol amendments**
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5 456 Protocol amendments will be documented with a description of the
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7 457 change and the date of the change.
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12 459 **Study status**
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14 460 Subject recruitment is underway, started at November 2019, but the first
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16 461 inclusion was in January 2020. To date, eight patients were enrolled. The
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18 462 recruitment period spans over October 2020 with the goal to include 21 patients
19
20 463 per treatment group, each patient completing the rehabilitation program and
21
22 464 evaluation before, after and 8 weeks later.
23
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25 465

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27
28 466 **Acknowledgements**
29

30 467 This Study was financed in part by the Coordenação de Aperfeiçoamento
31
32 468 de Pessoal de Nível Superior – Brasil (CAPES) – Doctorate's degree
33
34 469 scholarship, Finance Code 001.
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39 471 **Authors' contributions**
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41
42 472 NPOSB led the study design and wrote the manuscript. BFLF, CSPM,
43
44 473 TSR, TFC, FACC have made substantial contributions to the design of the
45
46 474 study. NPOS, BFLF participate in the patient recruitment, and data collection.
47
48 475 All the authors reviewed and approved the manuscript.
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50 476

51
52 477 **Funding**
53

54 478 The authors have not declared a specific grant for this research from any
55
56 479 funding agency in the public, commercial or not-for-profit sectors.
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2
3 480 **Competing interests**

4
5 481 None declared.
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For peer review only

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3 682 **Figure Legends**
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7 684 **Figure 1.** Schedule of enrollment, interventions, and assessments. Legend: t_1

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14 687 **Figure 2.** The schematic study design.
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For peer review only

TIMEPOINT	STUDY PERIOD				
	Pre-treatment		Post-allocation	Post-treatment	
	$-t_1$	0	t_1 to t_{10}	t_{post10}	t_{18}
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
<i>Control Group</i>					
<i>Experimental Group</i>					
ASSESSMENTS:					
<i>Postural balance deficits</i>	X				
<i>Cognitive screening</i>	X				
<i>Spasticity</i>	X				
<i>Ability to walk</i>	X				
<i>Stroke severity</i>	X				
<i>Clinical and demographic data</i>		X			
<i>Cardiovascular parameter variables</i>		X	X	X	X
<i>Adverse symptoms, perceived effort and pain</i>			X		
<i>Postural balance</i>		X		X	X
<i>Gait speed and kinematic analysis</i>		X		X	X
<i>Cortical Activation Patterns</i>		X		X	X
<i>Functional independence</i>		X		X	X
<i>Quality of life</i>		X		X	X
<i>Motivation</i>				X	
<i>Adverse events</i>					X

Figure 1. Schedule of enrollment, interventions, and assessments. Legend: t_1 1st week, t_{10} 10th week, t_{post10} post-training, t_{18} 18th week.

170x224mm (300 x 300 DPI)

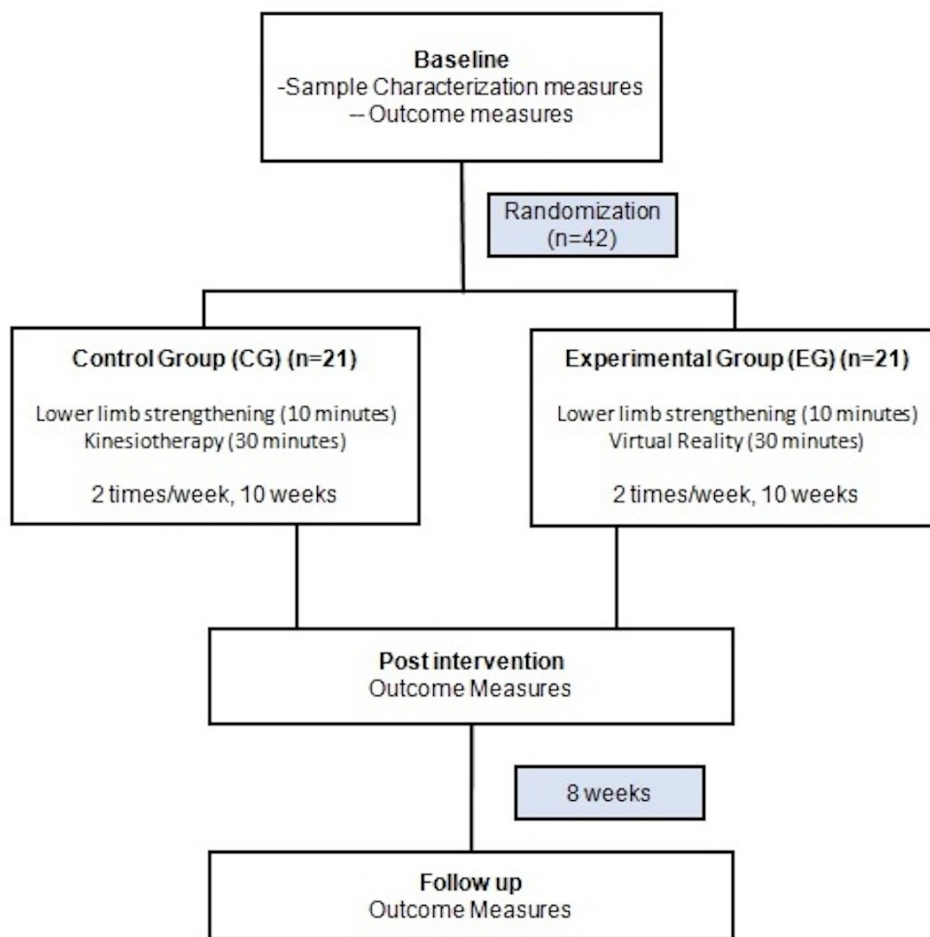


Figure 2. The schematic study design.

95x90mm (300 x 300 DPI)



Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2; 210
	2b	All items from the World Health Organization Trial Registration Data Set	20
	3	Date and version identifier	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1; 21
	5b	Name and contact information for the trial sponsor	21
	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	Not applicable
	5d	Composition, roles, and responsibilities of the coordinating centre, 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)	Not applicable
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	4-6

	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
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)	6; Figure 2
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	6; 7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-17; Table 1; Table 2; Table 3.
	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)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
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	10-13; Figure 1
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 1
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	7; 8

1				
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
5	Methods: Assignment of interventions (for controlled trials)			
6	Allocation:			
7	Allocation:			
8				
9	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 enrol participants or assign interventions	8
10				
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13				
14	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	8
15				
16				
17				
18	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
19				
20	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
21				
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
24				
25				
26	Methods: Data collection, management, and analysis			
27				
28	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	9-13
29				
30				
31				
32				
33		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	13; 17
34				
35				
36	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	8
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4	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	17-19
5				
6		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
7				
8		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)	19
9				
10				
11	Methods: Monitoring			
12				
13	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	Not applicable
14				
15		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	8
16				
17				
18	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	13
19				
20				
21	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
22				
23				
24				
25				
26	Ethics and dissemination			
27				
28	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
29				
30				
31	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)	21
32				
33				
34				
35	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
36				
37		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
38				
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4	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	20
5				
6	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
7				
8				
9	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	20
10				
11				
12	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	20
13				
14				
15	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	20
16				
17				
18				
19		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
20				
21		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
22				
23				
24	Appendices			
25				
26	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available if requested (not in protocol)
27				
28				
29	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	Not applicable
30				
31				

*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Effects of exergames training on Postural Balance in chronic stroke patients: study protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038593.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Aug-2020
Complete List of Authors:	Bessa, Nathalia; UFRN, Lima Filho, Bartolomeu; Federal University of Rio Grande do Norte, Department of Physical Therapy Medeiros, Candice; Federal University of Rio Grande do Norte, Department of Physical Therapy Ribeiro, Tatiana; Federal University of Rio Grande do Norte, Department of Physical Therapy; Federal University of Rio Grande do Norte Campos, Tânia; Federal University of Rio Grande do Norte, Department of Physical Therapy Cavalcanti, Fabrícia; Federal University of Rio Grande do Norte, Department of Physical Therapy
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine, Sports and exercise medicine
Keywords:	Stroke < NEUROLOGY, REHABILITATION MEDICINE, Neurology < INTERNAL MEDICINE

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1 **Effects of exergames training on Postural Balance in chronic**
2 **stroke patients: study protocol for a randomized controlled trial**

3
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16 **Date:** 11 Aug 2020

17
18 **Version:** 2

19
20 **Word Count:** 4282

1
2
3 **Abstract**
4

5
6 **Introduction:** Exergames training, as an additional therapy to standard care,
7
8 has been widely used for motor recovery after stroke patients, and it is a
9
10 valuable and positive tool in the rehabilitation of this population. This study
11
12 describes a single-blind randomized clinical trial that will aim to investigate the
13
14 effects of exergames training on postural balance in patients with chronic
15
16 stroke.
17
18

19 **Methods and analysis:** Forty-two individuals with chronic stroke (> 6 months),
20
21 aged 20 to 75 years, will be randomized into two groups: the experimental
22
23 group, which will be subjected to an exergames protocol, and control group,
24
25 which will undergo a kinesiotherapy protocol. Both protocols are based on
26
27 postural balance. The intervention will consist of 40-minute sessions twice a
28
29 week for 10 consecutive weeks. The volunteers will be evaluated before the
30
31 treatment, at the end of the interventions, and 8 weeks thereafter. The primary
32
33 outcome will be postural balance (Berg Balance Scale, Functional Reach Test,
34
35 Timed Up and Go test, and Center of Pressure variables), and secondary
36
37 outcomes will include gait (6-m timed walk and Kinovea Software), cortical
38
39 activation patterns (EEG Emotiv EPOC), functional independence (Functional
40
41 Independence Measure), quality of life (Stroke-Specific Quality of Life Scale),
42
43 and motivation (Intrinsic Motivation Inventory).
44
45
46
47
48

49 **Ethics and dissemination:** This protocol was approved by the Ethics
50
51 Committee of the Federal University of Rio Grande do Norte (number:
52
53 3.434.350). The results of the study will be disseminated to participants through
54
55 social networks and will be submitted to a peer-reviewed journal and scientific
56
57 meetings.
58
59
60

1
2
3 47 **Trial registration number:** RBR-78v9hx (Brazilian Registry of Clinical Trials –
4
5 48 ReBEC).

6
7 49 **Keywords:** Stroke, Randomized Controlled Trial, Postural balance,
8
9 50 Rehabilitation, Physical therapy modalities, Video Games.
10
11
12

13 51

14 52 **Strengths and limitations of this study**

- 15
16
17 53 • This study will explore objective data of postural balance and gait
18
19 54 through the force platform and kinematic analysis.
- 20
21
22 55 • This study is among the few that use EEG to assess brain activity in
23
24 56 stroke individuals undergoing an experimental protocol with exergames.
- 25
26 57 • The results of this research can lead to improvements in the use of
27
28 58 exergames for postural balance in stroke rehabilitation.
- 29
30
31 59 • This study should benefit participants not only in physical aspects but
32
33 60 also in psychological and social aspects.
- 34
35
36 61 • Blinding of participants will be not possible because of the nature of the
37
38 62 intervention.
39
40
41 63

64 Introduction

65 According to the World Health Organization, cerebrovascular disease
66 was the leading cause of death worldwide in 2016. Of those deaths, 5.78 million
67 were directly attributed to stroke, making it the main non-communicable cause
68 of death¹. In Brazil, stroke resulted in approximately 100,000 deaths in 2014²,
69 and data indicate that approximately 568,000 affected individuals suffer from
70 severe disability, making stroke the leading cause of disability in adults³.

71 Following stroke, various aspects of balance function are altered, such as
72 delay in regaining the ability to assume the standing posture, loss of balance,
73 asymmetry between the right and left limbs, increased postural sway, and
74 decreased weight bearing on the affected side^{4,5}. Postural balance is important
75 for functional tasks such as sitting, sit-to-stand, and walking. Dysfunction leads
76 to alterations in weight distribution patterns, causing the paretic leg to take less
77 load⁶. These changes increase the risk of falling, cause difficulties in executing
78 functional activities, and cause reduction in performance of daily living activities,
79 leading to a consequent reduction in social participation, which can aggravate
80 the clinical situation⁷.

81 Underuse of the impaired limb results in suppression of the cortical
82 representation of the affected limb and further inhibition of its use⁸. The
83 existence of cortical neural resources specialized in capturing changes in
84 postural stability, which have been detected by changes in
85 electroencephalography (EEG), supports the idea that postural adjustments are
86 not only due to muscle responses to disorders but also due to cortically
87 controlled intentional movements that may be altered following stroke⁹.

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3 88 One major component of stroke rehabilitation is exercise therapy,¹⁰ and
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5 89 motor skill learning is particularly attractive because practice-induced
6
7
8 90 improvement of sensorimotor performance supports the development of new
9
10 91 aptitudes, providing the flexibility to adapt to changing conditions¹¹.

12 92 From this perspective, exergames training has been widely used in
13
14 93 rehabilitation with the aim of improving sensorial, cognitive, psychological, and
15
16
17 94 motor function^{12,13}. They have been characterized as experiences that simulate
18
19 95 a real environment in which the user can interact with the scenario created by
20
21 96 the game through the involvement of multisensory aspects¹⁴. Exergames
22
23
24 97 applications have the potential to apply relevant concepts of neuroplasticity,
25
26 98 such as repetition, intensity, and task-oriented training of the paretic extremity⁷,
27
28 99 and may entrain several brain areas involved in motor planning and learning,
29
30
31 100 thus leading to an enhanced motor performance in rehabilitation^{12,15,16}.

32
33 101 There are some evidences to suggest the effectiveness of exergames in
34
35 102 improving upper limb function and balance as an additional therapy to standard
36
37 103 care in stroke patients. Therefore, therapy based on exergames is a valuable
38
39
40 104 and positive tool for the rehabilitation of this population^{17,18}.

41
42 105 A meta-analysis by Lee *et al.* (2019) found moderate evidence to support
43
44 106 the effect of exergames training on improved lower limb function, including
45
46 107 balance and gait, to a similar degree as upper limb function in chronic stroke
47
48 108 patients, suggesting that this technique may be used as a complementary
49
50
51 109 treatment method alongside traditional rehabilitation therapy. However, most of
52
53 110 the studies in this meta-analysis increased the overall treatment time by adding
54
55 111 exergames training to conventional treatment, which may be the reason for the
56
57
58 112 observed outcomes¹⁹.

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3 113 Considering the above evidence, it is paramount to investigate the
4
5 114 isolated effectiveness of exergames rehabilitation and its contributions to
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7
8 115 positive changes in postural balance in stroke patients, as this may provide
9
10 116 additional evidence for the rehabilitation process in this population. From this
11
12 117 perspective, it is hypothesized that training based on exergames improves
13
14 118 postural balance, cortical activation, functionality, quality of life, and motivation
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16
17 119 of patients with chronic stroke.

18
19 120 The purpose of this study to investigate the effects of exergames training
20
21 121 on postural balance in patients with chronic stroke and to explore changes in
22
23
24 122 cortical activation patterns, functionality, quality of life, and motivation.
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26
27 123

28 124 **Methods and Analysis**

29 125 **Design**

30
31 126 A single-blind randomized controlled clinical trial that follows the
32
33 127 recommendations of the Standard Protocol Items: Recommendations for
34
35 128 Interventional Trials (SPIRIT)²⁰ will be carried out (Figure 1). . Participants will
36
37
38 129 be randomized to receive the exergames protocol (experimental group, EG) and
39
40
41 130 kinesiotherapy protocol (control group: CG) (Figure 2).

42
43
44 131 [INSERT Image 1]

45 132 [INSERT Image 2]

46
47 133

48 49 134 **Participants**

50
51 135 The study population will consist of forty-two chronic stroke patients who
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53 136 live in the city of Natal or nearby. A volunteer selection will be carried out at the
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55 137 stroke patient care centers in the city. The selection can also be carried out via
56
57
58 138 spontaneous demand by the voluntary search of stroke patients after project
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3 139 advertisement on social media. After this, the first telephone contact will be
4
5 140 made to clarify any questions from the participants, and the first screening for
6
7 141 inclusion will be performed.
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9

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11 12 143 **Inclusion and exclusion criteria**

13
14 144 The participants will be selected according to the following criteria: (1)
15
16 145 first episode of unilateral stroke (ischemic or hemorrhagic); (2) postural balance
17
18 146 deficits (Berg Balance Scale score -BBS) <45 ²¹; (3) injury time ≥ 6 months; (4)
19
20 147 age between 20 and 75 years; (5) at maximum level 2 of the modified Ashworth
21
22 148 Scale to assess the spasticity of the paretic lower limb²²; (6) good cognitive
23
24 149 status based on the Mini-Mental State Examination (MMSE) (≥ 19 for illiterate,
25
26 150 ≥ 24 for literate)²³; (7) ability to walk without personal assistance indoors
27
28 151 (Functional Ambulation Category -FAC) scores ≥ 3 ²⁴; (8) clinically stable, with
29
30 152 no history of epilepsy or seizures in the last 6 months; (9) not having signs of
31
32 153 unilateral neglect or sensory or global aphasia as assessed by National Institute
33
34 154 Health Stroke Scale -NIHSS)²⁵; (10) no uncorrected hearing and/or visual
35
36 155 impairments; (11) not participating in a balance treatment protocol; and (12)
37
38 156 ability to understand and obey simple motor commands.
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44 157 Exclusion criteria will include (1) presenting other clinical conditions
45
46 158 affecting balance and (2) pregnancy.
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50 51 160 **Sample Size**

52
53 161 Using an online calculator²⁶ and based on previous study values
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55 162 (51.0 ± 4.6 and 46.2 ± 5.7)²⁷, a total sample of 42 participants (21 in EG and 21 in
56
57 163 CG) will be sufficient to detect a clinically important difference between the
58
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3 164 groups on the BBS. A statistical power of 80%, an alpha of 5% and a loss rate
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5 165 of 10% were considered for the sample calculation.
6
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10 167 **Randomization and blinding**
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12
13 168 A randomization sequence will be generated by a computer²⁸ in 3 blocks
14
15 169 of 12 participants and 1 block of 6 participants, allowing participants to be
16
17 170 equally distributed between the 2 groups. This stage will be conducted by a
18
19 171 researcher who is not involved in the study, they will keep the randomization list
20
21 172 confidential until the end of the study, and will organize the allocation in
22
23 173 sequentially numbered opaque envelopes. These envelopes will be sealed, and
24
25 174 the randomization sequence will be enforced using color coding for the study
26
27 175 groups (blue and red), that will correspond to the protocol that will be executed.
28
29 176 The contents of each envelope will be revealed at the beginning of each
30
31 177 patient's training by the study therapists responsible for the intervention to
32
33 178 maintain allocation confidentiality. The same therapists involved in CG training
34
35 179 will perform training in the EG. The researcher responsible for evaluations will
36
37 180 be blinded to all intervention groups. The only variables that will be collected
38
39 181 during the training will be evaluated by the study therapists (non-blind).
40
41 182 Statistical analysis will be performed by a blind researcher who will treat the
42
43 183 groups according to color, and the equivalence between groups and colors will
44
45 184 be revealed upon completion of the statistical analysis. The main researcher will
46
47 185 have access to the final trial dataset; this researcher will decide on terminating
48
49 186 the trial. All information about participants will be confidentiality before, during,
50
51 187 and after the trial.
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189 **Evaluation procedures**

190 The researchers will be trained before data collection procedures to
191 ensure reliability of measurements, and the participants will be submitted to
192 assessment using all the instruments mentioned below.

194 **Measures**

195 **Sample characterization measures**

- 196 • Cognition: The MMSE is a validated instrument in Brazil used to assess
197 cognitive function. The total score ranges from 0 to 30 points, and the
198 higher the score, the better the cognitive ability. Values are interpreted
199 according to educational status. Good cognitive status is considered with
200 scores of 24 points or higher for literate persons and 19 or higher for
201 illiterate persons²³.
- 202 • Ability to walk: This will be evaluated by the FAC, which is a sensitive
203 and reliable instrument for gait evaluation in stroke patients with
204 hemiparesis²⁴ and ranks the ability to walk according to the amount of
205 physical support required for the task. The score can vary from 0 (unable
206 to walk or needs the help of 2 therapists) to 5 (independent in
207 locomotion).
- 208 • Spasticity: The modified Ashworth scale allows the subjective
209 assessment of muscle tone and classifies the affected segments from 0
210 (normal tone) to 5 (rigid affected part)²².
- 211 • Clinical and demographic data: Personal, anthropometric, demographic,
212 and pathological data (including, injury time, paretic side, stroke type),

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3 213 and clinical history (history of falls, physical therapy treatment, and
4
5 214 previous use of exergames) will be collected.
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8 215 • Neurological impairment: NIHSS is a specific instrument to assess the
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10 216 severity of stroke via 10 items, and has been reported to have excellent
11
12 217 validity and reliability²⁵.
13
14

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17 219 **Outcome measures**

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19
20 220 All outcome measures will be assessed in both intervention groups. The
21
22 221 primary outcome measures considered in this study are as follows:
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24 222 **Postural Balance:**

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26 223 • Berg Balance Scale: BBS is a valid and reliable instrument for measuring
27
28 224 both the static and dynamic aspects of balance in people after stroke.
29
30 225 BBS scores range from 0 to 56, and values below 45 points are
31
32 226 predictive of falls, indicating a significant change in balance^{21,29}. In the
33
34 227 present study, test scores with the paretic limb positioned behind will be
35
36 228 used in item 13 and unipodal support over the paretic limb will be used in
37
38 229 item 14, minimizing the ceiling effect in individuals with better balance³⁰.
39
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41
42 230 • Functional Reach Test (FRT): FRT assesses a patient's stability by
43
44 231 measuring the maximum forward distance an individual can reach while
45
46 232 standing in a fixed position. It is widely used to identify the risk of
47
48 233 falling³¹. Displacements < 15 cm indicate patient fragility and risk of
49
50 234 falls³².
51

52
53 235 • Timed up and Go (TUG) test: It is a valid instrument for assessing
54
55 236 mobility and functional balance involving power, speed, and agility³³.
56
57 237 Performing the test within 10 seconds is considered normal for healthy,
58
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3 238 independent adults without the risk of falls. Values from 11 to 20 seconds
4
5 239 are expected for disabled or frail elderly people with partial independence
6
7 240 and a low risk of falls. Values > 20 seconds suggest significant physical
8
9 241 mobility deficits and risk of falls³⁴.

11 242 Center of Pressure (CoP) variables: Data for total displacement,
12
13 243 anteroposterior, and midlateral velocity of the CoP will be assessed using
14
15 244 the gold standard equipment for balance assessment, the force platform
16
17 245 (FP)³⁵. The Bertec® model 4060 connected to an external amplifier
18
19 246 (Bertec® AM651X) will be used.
20
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25
26 248 The secondary outcome measures considered in this study are as follows:
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28 249

30 250 **Cortical Activation Pattern**

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32
33 251 Alpha and beta waves will be evaluated based on their relationship with
34
35 252 the motor learning process³⁶, using the Emotiv EPOC® portable 14 sensor
36
37 253 electroencephalography (EEG) device, a gyroscope capable of detecting
38
39 254 changes in the movement performed.
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42 255

44 256 **Gait kinematic analysis**

45
46
47 257 The spatiotemporal and angular gait variables will be evaluated using the 6-
48
49 258 m timed walk test and Kinovea® software.

- 50
51 259
- 52 • Six-meter timed walk (6MTW): It is a valid and reliable test for the
53
54 260 assessment of the walking ability of patients with stroke³⁷. Gait speed
55
56 261 should be self-selected and considered comfortable and usual for the
57
58
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1
2
3 262 participant. Studies show variation in mean habitual speed (0.45 m/s -
4
5 263 0.78 m/s) of gait in individuals with hemiparesis^{38,39}.

6
7
8 264 • Software Kinovea®: Kinematic evaluation will be performed during gait
9
10 265 video capture (6MTW) using the Sony DCR-DVD850 digital cam, 2.7/6.7
11
12 266 cm LCD screen, and 60x optical zoom. Data will later be exported to
13
14 267 Kinovea® 0.8.15 software for paretic lower limb angle and gait speed
15
16
17 268 analysis. This is a public domain video editing and analysis software that
18
19 269 is valid, reliable, and capable of accurately measuring distances up to 5
20
21 270 m from the object⁴⁰.

22
23
24 271

25 26 272 **Functional independence**

27
28 273 The Functional Independence Measure (FIM) scale is used because of
29
30 274 its reliability, validity, precision, and feasibility criteria. It is composed of 18
31
32 275 items, including motor and cognitive items. Here the patient's answers are
33
34 276 valued from 1 (total dependent) to 7 (complete independence), and the total
35
36 277 punctuation ranges between 18 and 126. For this research, the FIM will be
37
38 278 applied exclusively to the motor items, limiting the minimum score to 13 and the
39
40 279 maximum to 91 points⁴¹.

41
42
43
44 280

45 46 281 **Quality of life**

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48
49 282 Quality of life perception will be assessed through a quality-of-life
50
51 283 assessment scale for stroke (Stroke-Specific Quality of Life Scale [SS-QoL]). It
52
53 284 is valid and reliable in assessing the quality of life after stroke in the Brazilian
54
55 285 population and has 49 items distributed over 12 domains⁴².

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287 **Motivation**

288 The intrinsic motivation inventory (IMI) is a multidimensional
289 measurement with 6 subscales used to assess the subjective experiences of
290 participants when developing an activity and attends to the reliability and validity
291 criteria. According to the inventory, instruction participants ranked their
292 agreement with each statement on a Likert scale of 1 (“not at all true”) to 7
293 (“very true”)⁴³.

294

295 **Participant monitoring measures**

296 Participants will be monitored during interventions using the following
297 measures:

- 298 • Cardiovascular parameter variables: Heart rate (HR) will be checked
299 using a portable oximeter and blood pressure (BP) using a
300 sphygmomanometer (Visomat Comfort III®, Incoterm, São Paulo, Brazil) on
301 the non-paretic arm.
- 302 • Adverse symptoms, perceived effort, and pain: Information regarding
303 headache, vomiting, and dizziness will be collected. Quantification of
304 perceived effort and pain will be used as indicators to monitor exercise
305 tolerance through the CR-10 (Category-Ratio Scale) Borg Scale⁴⁴ modified
306 by Foster *et al.* ⁴⁵ (2001).

307

308 **Adverse events**

309 Additional information such as hospitalizations, falls, out-of-routine
310 medical consultation, medication change, new diagnosis, and presence of
311 adverse events will be collected during the follow-up.

312

313 **Interventions**

314 The protocols in both groups will be performed individually through 40-
 315 minute sessions twice a week for 10 weeks (total of 20 sessions), totaling 13
 316 hours of intervention^{12,17,46}. The same outcome measures and motivation will be
 317 collected again at the end of the interventions (post-training) and after 8 weeks
 318 of the end of the interventions (follow-up). All participants will be instructed not
 319 to perform any other physical activity that works on body balance during the
 320 study period.

321 During each session, absences, manifestations of adverse symptoms,
 322 and occurrence of imbalance and/or falls will be recorded. Interventional
 323 modifications will be performed according to the patient's level of adaptation
 324 involving optimization of time or number of repetitions, and/or rest time
 325 enlargement, and all will be registered.

326 Both groups will begin their protocols with adapted lower limb strength
 327 training for 10 minutes^{47,48} as described in Table 1. Each exercise should be
 328 performed with respect to the patient's level of adaptation and evolution will
 329 occur in the 6th and 13th sessions using the materials described.

330

331 **Table 1.** Lower limb strengthening exercises.

Exercise	Evolution	Materials Used	Sets
1. Get up and sit on a chair	Surface change	1 or 2 mats to create an unstable surface (H: 3 x W: 43 x L: 93 cm).	2 sets of 60 seconds with 30 seconds of rest
2. Go up and down steps	Increase the step height; add weight	Larger step and 1 kg shin pad.	
3. Strengthening of hip extensors	Add weight	1 kg and 2 kg shin pad.	

4. Tiptoe rise Add weight 1 kg and 2 kg shin pad.

332 Source: Adapted from Allet et al. (2010).

333

334 **Control Group**

335 Participants in the CG will receive a kinesiotherapy protocol (30 minutes)
 336 (Table 2), focusing on balance based on previous studies, and that promotes
 337 stimuli similar to the EG, selected so they demand identical motor sensors in
 338 both intervention environments, real and virtual⁴⁷⁻⁵⁰. Two progressions will
 339 happen, in the 6th and 13th sessions.

340

341 **Table 2.** Kinesiotherapeutic protocol exercises.

Exercise	Evolution	Materials Used	Sets**
1. Gait training on a stable surface.	Gait training on an unstable surface using mats; addition of shin pads of 1 kg.	Mat* and 1 kg shin pads.	2 sets of 3 minutes
2. Laterolateral weight transfer and discharge.	Addition of 1 and 2 mats respectively.	Mat	3 sets of 60 seconds
3. Anteroposterior weight transfer and discharge.	Addition of 1 and 2 mats respectively.	Mat	3 sets of 60 seconds
4. Laterolateral cephalic movement with eyes open.	Same movement with eyes closed. Added an exercise mat.	Mat	3 sets of 60 seconds
5. Anteroposterior cephalic movement with eyes open.	Same movement with eyes closed. Added an exercise mat.	Mat	3 sets of 60 seconds
6. Dissociation of scapular and pelvic girdles.	Addition of 1 and 2 mats respectively.	Mat	3 sets of 2 minutes

342 Source: Adapted from Nascimento, Patrizzi, Oliveira (2012); Soares, Sachelli (2008);
 343 Allet et al. (2010) e Ribeiro (2015). Legend: *The mats (height: 3 x width: 43 x length:
 344 93 cm) will be used to create an unstable surface; **For each series performed, the
 345 participant will be entitled to 30 seconds of rest.

346

1
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3 347 **Experimental Group**
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5 348 Participants in the EG will receive seven Wii Fit Plus exergames on the
6
7 349 Nintendo Wii® (30 minutes) (Table 3). This will use the Wii Balance Board
8
9 (WBB) accessory, a multimedia projector, and the Wii Remote Controller.
10 350
11
12 351 Initially, participants will have a moment to adapt to Nintendo Wii and its
13
14 352 components. It is expected that the participants in this group will be able to deal
15
16 353 satisfactorily with the games used in the protocol after adaptation. Otherwise,
17
18 354 they will enter the non-adherence criteria.
19
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23
24 356 **Table 3.** Exergames protocol exercises.

Game	Description	Progression
1. Free Run	Control in patient's pocket "marching" on firm surface	Addition of 1 and 2 mats* respectively
2. Soccer Heading	On WBB; performs anteroposterior and laterolateral weight transfer to virtually "hit" the head on the ball, with an attempt of 180 s and a throw of 80 balls	Addition of 1 and 2 mats respectively
3. Pinguim Slide	On WBB; performs laterolateral weight transfer in order to "catch" the largest number of fish, with 3 attempts of 60 s	Addition of 1 and 2 mats respectively
4. Ski Slalom	On WBB; performs laterolateral weight transfer for the purpose of deflecting obstacles, and anteroposterior weight transfers to control speed while skiing on the mountain, with three 60-s attempts	Addition of 1 and 2 mats respectively
5. Table Tilt	On WBB; performs small laterolateral and anteroposterior displacements as a simulation of an unstable board to place the balls inside holes, with 3 attempts of initial 30 s. You gain 20 s every 1 level you reach so that you do not exceed 180 s	Addition of 1 and 2 mats respectively
6. Free Steps	Up and down WBB, alternating feet with eyes open for 180 s	Addition of weights of 1 kg and 2 kg, respectively

7. Balance Bubble	On WBB; performs laterolateral and anteroposterior body displacement without the bubble touching the banks of the virtual river for 180 s	Addition of 1 and 2 mats respectively
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357 Legend: Each game will be executed for 3 minutes with a rest interval of approximately
358 1 minute; *The mats (height: 3 × width: 43 × length: 93 cm) will be used to create an
359 unstable surface.
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361 The games were pre-established with focus on balance, and demands
362 similar to that of the kinesiotherapy protocol: saccadic stimulation,
363 visuovestibular cephalic movement, proprioceptive stimulus, dynamic balance
364 training, static gait, ankle and hip strategies, fine CoP control, stimulus
365 optokinetic, double task (motor), and motor coordination⁵¹⁻⁵³. All scores
366 obtained in games will be noted. Progression will occur upon adaptation of the
367 patient, 2 evolutions will occur, in the 6th and 13th sessions.

369 Adherence

370 Participants will be contacted by telephone to confirm assessment and
371 training sessions to avoid sample loss. Strategies to improve adherence include
372 making up for missed sessions and interventions of motivated professionals.
373 Regardless of the protocol, the criteria for non-adherence will be considered as
374 follows: (1) absence > 30% of the intervention, consecutively and without make-
375 up sessions; (2) presenting persistent pain or severe discomfort (headache,
376 vomiting, dizziness, etc.), which prevents continuity in performing the proposed
377 protocol in future sessions (or both); (3) presenting hemodynamic instability:
378 decompensation of systemic arterial pressure (systolic and diastolic values >
379 200 mmHg and 110 mmHg, respectively)⁵⁴ and HR above the submaximal
380 values allowed during the training maintained even after pauses, calculated by

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3 381 means of the formula $[HR_{sub} = 0.75 \times (220 - age)]^{55}$; and (3) those who did not
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5 382 adapt to the proposed intervention.
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10 384 **Data acquisition**

11
12 385 For data collection of the CoP variables, 6 static balance tests will be
13
14 386 performed on the FP based on their complexity variation and common use in
15
16 387 the literature^{56,57}: bipodal support on a stable surface with eyes open and eyes
17
18 388 closed for 30 s each; unipodal support of paretic limbs on a stable surface with
19
20 389 eyes open and eyes closed for 30 s each; unipodal support of non-paretic limb
21
22 390 on a stable surface with eyes open and eyes closed for 10 s each. The distance
23
24 391 between the patients' feet will be standardized⁵¹ and in unipodal support tasks,
25
26 392 the contralateral knee may be slightly flexed, and there may be no contact
27
28 393 between the raised and support legs. Each test can have 1 successful attempt
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30 394 and a maximum of 3 unsuccessful attempts. The attempt is considered invalid if
31
32 395 the participant moves their support leg or touches the floor with the contralateral
33
34 396 leg⁵⁸.
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40 397 For gait analysis during 6MTW, the camera will be positioned
41
42 398 perpendicular to the plane of motion, at a height of 1 m and 3 m away from the
43
44 399 subject to capture the gait pattern of the hemiparetic side, and will be
45
46 400 considered as a complete gait cycle. Markers will be placed on the main bone
47
48 401 references of the paretic lower limb (greater trochanter of the femur, lateral tibial
49
50 402 condyle, lateral fibular malleolus, fifth metatarsal head, and lateral calcaneal
51
52 403 bone tuberosity) for further analysis.
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56 404 For encephalographic recording during the FP static balance and walking
57
58 405 tests, the Emotiv Epoc headset will be positioned on the user's head according
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3 406 to the international placement in the 10-20 positioning system following the
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5 407 manufacturer's specifications⁵⁹.
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11 410 **Data processing**

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14 411 The Bertec® Model 4060 platform will be synchronized with Qualisys
15
16 412 Motion Capture Systems (Qualisys Medical AB, 411 13 Gothenburg, Sweden),
17
18 413 and through that system software, Qualisys Track Manager, data for CoP will be
19
20 414 collected and converted to MATLAB compatible files (Mathworks, Natick, RI,
21
22 415 USA). The sampling rate will be 40 Hz, and a Butterworth bandpass filter with a
23
24 416 cutoff frequency of 15 Hz will be applied to eliminate noise contamination.
25
26
27

28 417 For kinematic analysis, the videos will be converted to an Audio Video
29
30 418 Interleave (AVI) file extension and exported to Kinovea software. The hip, knee,
31
32 419 and dorsiflexion flexion angles will be evaluated in the middle oscillatory phase
33
34 420 of gait, using the following joints: hip, tibiofemoral metatarsophalangeal, and
35
36 421 calcaneal. Emotiv EPOC data processing will follow the model used by Oliveira
37
38 422 *et al.*⁶⁰ (2018). The encephalographic recording will take place during gait and
39
40 423 static balance tests, using 10 s of single-leg support activity and a central 10-s
41
42 424 cutout in bipodal support activities.
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49 426 **Statistical analysis**

50
51 427 The SPSS (Statistical Package Social Science) V.21.0 software program
52
53 428 will be used, and a significance level of 5% and CI of 95% will be implemented
54
55 429 for all statistical analyses. A descriptive analysis of the sample characterization
56
57 430 variables will be performed through central tendency and dispersion measures.
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3 431 Normality tests (Kolmogorov-Smirnov) will be used for outcomes and will
4
5 432 be compared between groups within each training session by using intergroup
6
7 433 comparisons, t tests for independent samples, or Mann–Whitney U tests. A
8
9 434 mixed analysis of variance (ANOVA) with repeated measures will be used to
10
11 435 compare values and variations of outcome measures, comparing values
12
13 436 between groups and between baseline, post-training, and follow-up
14
15 437 assessments.

16
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18
19 438 The effect size will be calculated using GPower 3.1.9.3 (University of
20
21 439 Dusseldorf, Kiel, Germany). Cohen's d will be used to calculate the effect size
22
23 440 between the control and the experimental groups, and the partial eta squared
24
25 441 for intragroup analyzes⁶¹. Intention-to-treat analysis will be performed for
26
27 442 dropout data, considering the last data obtained from the participant.
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31 443

32 33 444 **Risk of Bias and Study Limitation**

34
35 445 The present study has a low risk of selection bias due to randomization
36
37 446 and concealment of the allocation of participants; low risk of detection bias as
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39 447 the outcome assessor will be blind; high risk of performance bias because the
40
41 448 participants will not be blind to the proposed therapies; reporting and attrition
42
43 449 biases do not apply because it is a protocol study⁶².

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45
46 450 The proposed follow-up time (8 weeks) can be considered a potential
47
48 451 (minor) study limitation; it is not verified whether motor and neurophysiological
49
50 452 changes resulting from the proposed intervention will be maintained over a long
51
52 453 term (1 year). However, it is suggested that the effect of treatment with
53
54 454 Nintendo Wii can be maintained for at least 2 months after the intervention, with
55
56 455 improvements in motor recovery.
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456 **Patient and public involvement**

457 Patients were not involved in the design of this trial, establishing the
458 research question, or developing recruitment procedures. At the end of the
459 study, the results will be reported to the participants in form of a lecture,
460 showing the effects found in the studied variables. The results of the study will
461 be disseminated to participants through social networks and will be submitted to
462 a peer-reviewed journal and scientific meetings.

464 **Ethics and dissemination**

465 This research was approved by the Research Ethics Committee of the
466 Federal University of Rio Grande do Norte, with protocol number 3.434.350 on
467 July 3, 2019 and trial registration number RBR-78v9hx (Brazilian Registry of
468 Clinical Trials). Participants will be informed of the study objectives, its risks and
469 benefits, and when eligible for inclusion, if they agree to participate, must sign
470 the informed consent before the study begins. They will be free to abandon the
471 study at any time without the obligation to give any explanation.

472 There will be prior contact with individuals through social networks, when
473 all information about the study will be presented as well as the Resolution No.
474 466/2012 of the Brazilian National Health Council of 2012, which provides
475 guidelines and standards for research involving human participants. In case any
476 negative effects occur, participants who suffer harm from trial participation will
477 receive physical assistance according to the injury. The study results will be
478 disseminated to participants through social networks and will be submitted to
479 peer-reviewed journals and scientific meetings.

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3 481 **Protocol amendments**
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5 482 Protocol amendments will be documented with descriptions of the
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7 483 change and the date of the change.
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12 485 **Study status**
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14 486 Subject recruitment is underway, started in November 2019, but the first
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16 487 inclusion was in January 2020. To date, eight patients were enrolled in the
17
18 488 study. The recruitment period spans till January 2021. The goal is to include 21
19
20 489 patients per treatment group, each patient completing the rehabilitation program
21
22 490 and evaluation before and after, and 8 weeks later.
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26 491

27
28 492 **Acknowledgements**
29

30 493 This study was financed in part by the Coordenação de Aperfeiçoamento
31
32 494 de Pessoal de Nível Superior – Brasil (CAPES) – Doctorate's degree
33
34 495 scholarship, Finance Code 001.
35
36

37 496

38
39 497 **Authors' contributions**
40

41
42 498 NPOSB led the study design and wrote the manuscript. BFLF, CSPM,
43
44 499 TSR, TFC, and FACC have made substantial contributions to the design of the
45
46 500 study. NPOSB and BFLF participate in participants' recruitment and data
47
48 501 collection. All authors reviewed and approved the manuscript.
49
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51 502

52
53 503 **Funding**
54

55
56 504 The authors have not declared a specific grant for this research from any
57
58 505 funding agency in the public, commercial, or not-for-profit sectors.
59
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3 506 **Competing interests**
4

5 507 None declared.
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3 716 **Figure Legends**
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7 718 **Figure 1.** Schedule of enrollment, interventions, and assessments. Legend: t_1
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9 719 1st week, t_{10} 10th week, $t_{\text{post}10}$ post-training, t_{18} 18th week.
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14 721 **Figure 2.** The schematic study design.
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For peer review only

TIMEPOINT	STUDY PERIOD				
	Pre-treatment		Post-allocation	Post-treatment	
	$-t_1$	0	t_1 to t_{10}	t_{post10}	t_{18}
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
<i>Control Group</i>					
<i>Experimental Group</i>					
ASSESSMENTS:					
<i>Postural balance deficits</i>	X				
<i>Cognitive screening</i>	X				
<i>Spasticity</i>	X				
<i>Ability to walk</i>	X				
<i>Stroke severity</i>	X				
<i>Clinical and demographic data</i>		X			
<i>Cardiovascular parameter variables</i>		X	X	X	X
<i>Adverse symptoms, perceived effort and pain</i>			X		
<i>Postural balance</i>		X		X	X
<i>Gait speed and kinematic analysis</i>		X		X	X
<i>Cortical Activation Patterns</i>		X		X	X
<i>Functional independence</i>		X		X	X
<i>Quality of life</i>		X		X	X
<i>Motivation</i>				X	
<i>Adverse events</i>					X

Figure 1. Schedule of enrollment, interventions, and assessments. Legend: t_1 1st week, t_{10} 10th week, t_{post10} post-training, t_{18} 18th week.

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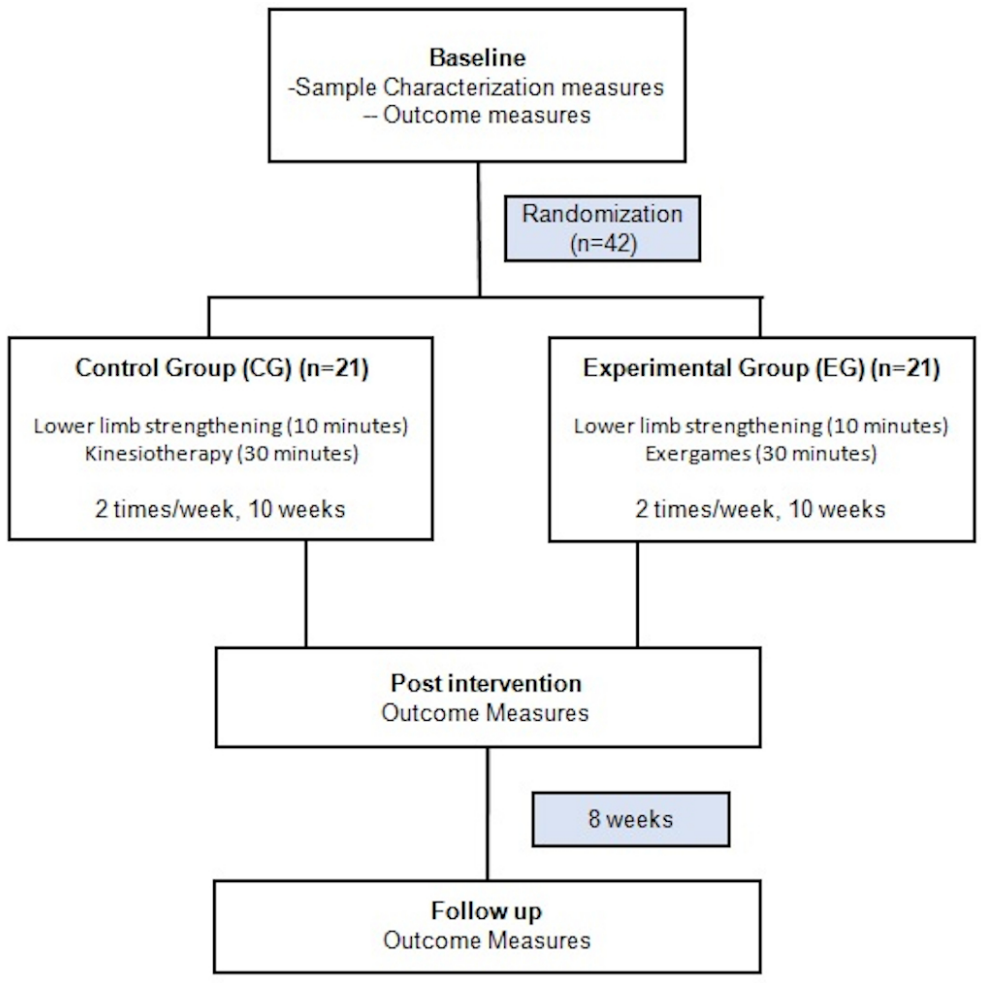


Figure 2. The schematic study design.

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Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2; 210
	2b	All items from the World Health Organization Trial Registration Data Set	20
	3	Date and version identifier	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1; 21
	5b	Name and contact information for the trial sponsor	21
	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	Not applicable
	5d	Composition, roles, and responsibilities of the coordinating centre, 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)	Not applicable
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	4-6

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4		6b	Explanation for choice of comparators	4-6
5	Objectives	7	Specific objectives or hypotheses	6
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7	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)	6; Figure 2
8				
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10				
11	Methods: Participants, interventions, and outcomes			
12				
13	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	6; 7
14				
15	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
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18	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-17; Table 1; Table 2; Table 3.
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22		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)	14
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25		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17
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28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
29				
30	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	10-13; Figure 1
31				
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34	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 1
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37	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	7; 8
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
5	Methods: Assignment of interventions (for controlled trials)			
6	Allocation:			
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9	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 enrol participants or assign interventions	8
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14	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	8
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18	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
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21	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
24				
25				
26	Methods: Data collection, management, and analysis			
27				
28	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	9-13
29				
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33		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	13; 17
34				
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36	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	8
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4	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	17-19
5				
6		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
7				
8		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)	19
9				
10				
11	Methods: Monitoring			
12				
13	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	Not applicable
14				
15		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	8
16				
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18	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	13
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21	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
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26	Ethics and dissemination			
27				
28	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
29				
30				
31	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)	21
32				
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34				
35	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
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37		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
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4	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	20
5				
6	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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9	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	20
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12	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	20
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15	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	20
16				
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19		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
20				
21		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
22				
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24	Appendices			
25				
26	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available if requested (not in protocol)
27				
28				
29	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	Not applicable
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*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.