

# BMJ Open Study protocol of a randomised controlled trial for the effectiveness of a functional partial body weight support treadmill training (FPBWSTT) on motor and functional skills of children with ataxia

Alexandra Lepoura <sup>1</sup>, Sofia Lampropoulou,<sup>2</sup> Antonis Galanos,<sup>3</sup> Marianna Papadopoulou,<sup>1</sup> Vasiliki Sakellari<sup>1</sup>

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<sup>1</sup>Physiotherapy, University of West Attica, Egaleo, Greece

<sup>2</sup>Physiotherapy, University of Patras School of Health Sciences, Patras, Greece

<sup>3</sup>Laboratory for Research of the Musculoskeletal System, National and Kapodistrian University of Athens Faculty of Medicine, Athens, Greece

## Correspondence to

Mrs Alexandra Lepoura;  
[alepoura@uniwa.gr](mailto:alepoura@uniwa.gr)

## ABSTRACT

**Introduction** A great heterogeneity characterises the paediatric population with ataxia, which has been studied poorly. The lack of postural control and coordination, in addition with features of the 'ataxic' gait are linked with functional limitations. Studies on physiotherapy interventions for children with ataxia are highly needed for identifying optimal training strategies for improving motor and functional related skills.

**Methods and analysis** A stratified randomised control clinical trial of a 4-week functional partial body weight support treadmill training, (5 days/week 45 min/day) and 2-month follow-up period will be applied in children with ataxia, aged 8–18 years old with Gross Motor Function Classification System II–IV. Participants will be allocated to experimental group (intervention and usual care) or control group (usual care), using stratified randomisation process into two strata (progressive and non-progressive ataxia). Participants will be assessed at baseline, by the end of the 4-week period and by the end of a 2-month period as a follow-up measurement. Motor and functional skills will be assessed using the Gross Motor Function Measure-D and E, the Pediatric Balance Scale, the 10-meter walk test, the 6-minute walk test, the Scale for Assessment and Rating Ataxia, the timed up and go test and children's spatiotemporal gait features will be assessed through GaitSens software recording over a 2 min low treadmill gait speed, while three-dimensional gait analysis will be performed for kinetic and kinematic analysis of the lower limbs in all three levels of movement. Two-way mixed Analysis of Variance (ANOVA) with factors 'intervention' (between group) and 'time' (within group) will be used for the analysis of all parameters. Analysis of Covariance (ANCOVA) will be used in case of imbalance of baseline measurements. Statistical significance will be set at  $p < 0.05$  using the statistical package SPSS V.21.00.

**Ethics and dissemination** University of West Attica (study's protocol: 14η/26-04-2021) and 'ATTIKON' General University Hospital of Athens (study's protocol: Γ ΠΑΙΑ, ΕΒΔ 149/20-3-2020). Trial results of the main trial will be

## Strengths and limitations of this study

- Heterogeneity will be taken into account through stratified sample, based on progressive and non-progressive type of ataxia.
- This Randomised controlled trial (RCT) will be the first to examine changes in spatiotemporal gait characteristics, kinetics and kinematics gait features in a 2-month follow-up period in children with ataxia.
- First study evaluating the effect of treadmill training accompanied with functional activities in such population.
- The lack of blinding in all assessors collecting data is a limitation of the study design.

submitted for publication in a peer-reviewed journal and/or international conference.

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## INTRODUCTION

Ataxia is a neuromotor disorder, which affects movement coordination and balance and is considered a quite common type of movement disorder in childhood.<sup>1</sup> The impact of lack of postural control and coordination is huge in individuals with ataxia, who have to face everyday activities with the risk of falling.<sup>2,3</sup> A great heterogeneity characterises children with ataxia. Based on history and clinical examination chronic types of ataxia can be either persistent (progressive or not progressive) or intermittent, while different causes, such as cerebellar tumour, metabolic disorder, cerebral palsy (CP), stroke and more can underlie the pathology behind ataxia.<sup>1</sup> The incidence of ataxia is estimated approximately 26/100 000 children in Europe and

probably reflects a minimal prevalence worldwide.<sup>4</sup> Ataxia in the paediatric population has been poorly studied in terms of both evaluation, but also in terms of intervention, according to a systematic review.<sup>5</sup>

In terms of evaluation, the Childhood Ataxia and Cerebellar Group of the European Pediatric Neurology validated the use of the Scale for Assessment and Rating Ataxia (SARA) in paediatric population which can be reliably assessed above the age of 8 years old.<sup>6,7</sup> While ataxia remains poorly understood, recent studies used SARA in an effort to correlate severity and underlying aetiology among the great heterogeneity of ataxia in children and adults with early onset ataxia and cerebral tumour.<sup>8,9</sup> Additionally, SARA scores have been correlated with gait features, such as the increased knee extension, which seems to provide a sensitive measure to detect progression of functionality in children and adolescents affected by Friedreich's ataxia.<sup>10</sup> Gait features in adults with cerebellar ataxia have been described in the literature through a systematic review and have been associated with the increased risk of fall which accompanies ataxic gait.<sup>11</sup> Data from ataxic spatiotemporal features and gait analysis refer to decreased cadence, step and stride length, increased step width, variability in gait measures and abnormalities in kinetics and kinematics features which may provide a sensitive measure for ataxia progression, but also indicate the 'instability' of ataxic gait pattern among the heterogeneity in the investigated population.<sup>10-13</sup> On the other hand pelvic stability<sup>10</sup> and improvements in spatiotemporal gait features may indicate reduction of risk of falling and improvements in functional motor skills, as reported in one case study in a child with ataxic CP and a pilot study in adolescent affected by ataxia due to acquired brain injury, after virtual reality interventions.<sup>12,14</sup>

The lack of studies on the effect of physiotherapy interventions on children with ataxia is clearly stated in a recent systematic review.<sup>4</sup> The study reported a total number of 40 children with ataxia, aged between 5 and 18 years old that have been included in studies of exercise and physical therapy interventions conducted the last two decades, while data were able to be extracted from a total of only 21 children with ataxia. According to the authors' findings of the included studies, walking ability was not consistently measured or described and the provided measurements could identify only short-term outcomes. Interesting was the variability of frequency, intensity and duration of the applied interventions which however indicated a median overall outcome that could be used as a general guide for implementation into future clinical practice. The authors' conclusions highlighted the urgent need for high-quality and child-focus studies, which would constitute optimal physiotherapy interventions for such population.

Impaired balance, coordination and pathological patterns of movement influence functional activities and reduce the level of performance in daily life according to studies on children with CP and individuals with ataxia.<sup>2,15</sup> Similarly, school-aged children with spastic diplegic CP

were reported as less physically active compared with their peers.<sup>16</sup> The same study added that children with CP would need approximately 2.5 hours/day of exercise to reach daily activity levels of peers. In typical development, children and teenagers experience a quite challenging environment with activity patterns engaged in bursts of intense walking and physical activity interspersed with varying intervals of low and moderate intensity.<sup>17</sup> Graded exposure to environmental challenges and high intensity of practice during gait has been proposed as rehabilitation strategies in order to consolidate motor learning and as a means for improving the reduced ability of adaptation to environmental changes, which characterises ataxic gait.<sup>2,18</sup>

Additionally in daily life, children in typical development demonstrate ability to perform dual-task, by dividing their attention between different tasks, without affecting their performance in none of them. In this notion, task characteristics, performed during gait play an important role through their demand or complexity, which can affect the gait parameters in typically developing children.<sup>19</sup> Recently a study indicated that dual-task training can be effective on improving postural control in children with infantile hemiparesis.<sup>20</sup> The relationship of dual task training and prevention of falls, postural control and gait improvement has been studied in adult stroke survivors and there are suggestions for implementation of such approaches in clinical physiotherapy practice.<sup>21-23</sup> Emphasis on training of two motor tasks, performed at the same time (motor dual task), over training of a motor and cognitive task, performed at the same time has been suggested as an important aspect of cognitive-motor interference for application in patients with neuromotor disorders.<sup>22</sup>

Improving motor and gait related functional skills that can be implemented into daily life are some of the biggest challenges for the effective treatment in neuromotor disorders. These challenges arise from the lack of ability to integrate safely evidence-based therapeutic approaches into physiotherapy practice. This is due to difficulties to maintain a balanced body posture, the simultaneous provision of techniques to enhance biomechanical and physiological motor patterns, and the safe challenge of the child to motor skills simulated by the needs of everyday life. The use of partial body weight support treadmill training (PBWSTT) as a means of training upright posture and gait has been increasingly used in recent years.<sup>24</sup> Relevant studies indicate that using such therapeutic approaches there is a safe training environment provision for both physiotherapist and patient, while practicing the whole process of walking on a continuous charge and upright aligned body position and possibility to apply other activities to strengthen functional skills related to everyday living activities.<sup>25,26</sup> The benefits and effectiveness of partial body weight support and treadmill training interventions that seem to be provided are related to the improvement of gross mobility in areas of standing and mobility skills from infancy to adolescence in neuromotor

paediatric disorders, according to the relevant systematic reviews.<sup>5 24 27</sup>

The variability of the protocols of the existing research highlights that partial body weight support and treadmill training intervention parameters should be standardised across trials of paediatric neuromotor groups, to allow suitable implementation into clinical practice. Child's and parents' expectations on real life challenges are an integral part of the therapeutic setting goal and conduction of rehabilitation programmes should meet the desired objectives. A paradigm shift for physiotherapy management from traditional to more focused intense and active training protocols has been proposed the latest years, as an evidence based mean of promoting activity and lifestyle modifications, which can alter positive impacts for the whole family.<sup>28</sup> It seems that creation of innovative rehabilitation programmes is essential, through integration of therapeutic approaches and intensity levels that are necessary for both provision of effective treatment in neuromotor disorders but also for the adjustments made through the needs imposed by modern society, in which children and parents interact.

### Study objective

The present study aims to assess the effectiveness of an innovative intensive therapeutic programme in relation to standard physiotherapy for children with ataxia. To address this aim the proposed study will develop a 4-week therapeutic programme—using partial body weight support on a treadmill in order to promote a close to normal pattern of gait of increased duration and safety and in parallel use motor dual task and functional training, simulating everyday activities environment in comparison to standard physiotherapy for children with ataxia.

The primary objective of the proposed protocol is to evaluate the effect of the proposed 4-week intensive therapeutic programme on motor tasks and functional skills related to standing and gait. We hypothesise that the suggested therapeutic functional programme is more effective than typical physiotherapy in improving gross motor function in standing and walking when applied in children with ataxia, aged between 8 and 18 years old.

Secondary objectives refers to evaluating the effect from the application of the proposed programme on functional skills in balance, self-selected cadence, dynamic balance control, physical condition and endurance, ataxia features and gait analysis characteristics. Further objectives of the study refer to the long-term effect of the 4-week therapeutic programme in a time period of 2 months and to understand the effect of such intervention and clinical interpreted its results for future therapeutic purposes.

## METHODS AND ANALYSIS

### Study design

This protocol describes a stratified randomised control clinical trial of a 4-week functional PBWSTT and 2-month follow-up period applied in children with ataxia. Children will be allocated to experimental (EG) or control group

(CG), using stratified randomisation method, based on progressive type of ataxia disorder and two strata will be used: the progressive and non-progressive type of ataxia.<sup>29</sup>

Intervention and assessment will take place in a private clinical setting of Athens, performed by the same physiotherapy team, while dimensional gait analysis will be assessed at the Gait and Motion Analysis Lab of the Hellenic Society for the Protection and Rehabilitation of the Disabled individuals (ELEPAP) of Athens. Recruitment of participants was initiated in June 2021 and will end in July 2022. It is anticipated that the trial will be completed by the end of September 2022. Intermediate cessation periods, due to COVID-19 pandemic will be reported and discussed with the end of the study.

### Patient and public involvement

No patient involved.

### Sample

Recruitment of participants will be obtained through clinician invitation at public healthcare faculties from which approval has been achieved by their Scientific Board (the Pediatric Clinics of the ATTIKON University Hospital and the ELEPAP of Athens). An invitation and information documents (approved by the Ethics Committee of the University of West Attica) will be published through social media and send through emails to organisations of ataxia in Greece, private paediatric physiotherapy faculties and other relative therapeutic institutes that possibly treat children with ataxia and provide services to their families.

### Inclusion criteria

1. Ataxia as their primary motor disorder, as a result of congenital, acquired or genetic damage.
2. Gross Motor Function Classification System (GMFCS) II–IV.
3. Age 8–18 years old.
4. Attendance of a physiotherapy programme in an outpatient or community setting the last 6 months after a relevant medical admission.
5. Willingness to participate in the study.

### Exclusion criteria

1. Invasive neurological or orthopaedic intervention, such as botox injection, alcohol block, muscle-tendon lengthening or tendon transfer surgery within 6 months from the study.
2. Coexisting degenerative disorders, such as arthrogyrosis.
3. Significant heart or respiratory disease.
4. Lower motor neurons' diagnosis, such as spinal muscular atrophy.
5. Comorbid conditions (not related to ataxia diagnosis) such as peripheral vascular disease and diabetic polyneuropathy.
6. Coexisting musculoskeletal and rheumatoid disorder that prevents independent walking.
7. Deficient and/or ocular alertness.

8. Cognitive impairments which restrict them from understanding commands, evidenced by their medical diagnosis or any kind of psychiatric disorder.
9. Reluctant parents to collaborate with the researchers for scheduling the timeframe of evaluations and/or intervention period.

### Allocation

Once parents and children have been informed of the whole process of the study and have agreed to participate, parents and children over the age of 16 years old will be asked to sign a consent form (online supplemental appendix I). A code will be given to each participant for securing deidentification in the following children's data completion. After enrolment, a randomisation table will be used for randomisation process. Sample will be stratified based on type of ataxia into two blocks, progressive and non-progressive ataxia. One of the main researchers will be responsible for generating the allocation procedure, which will be kept concealed from the rest of the research team. The other main researcher will be responsible for enrolment and assigning participants to the allocation group, either EG or CG. EG will follow the 4-week intervention programme in addition with their regular care and the CG will continue receiving their regular therapeutic programme (online supplemental figure 1).

### Outcomes

Demographic and anthropometric data, including the functional level of each child through use of GMFCS and data obtained by the Child Quality of Life Questionnaire for children report will be collected once in the baseline assessment.<sup>30 31</sup>

Primary and secondary outcomes will be assessed three times over a period of approximately 3 months. A first baseline assessment prior to the 4-week intervention period (pre), a 4-week post assessment, conducted by the end of the 4-week intervention period (4-week post) and a final 2 months postassessment, conducted 2 months by the end of the 4-week intervention period (follow-up) (table 1).

### Primary outcomes

- ▶ The Gross Motor Function Measure (GMFM-88) dimension D/E, will be expressed as percentage score (%) for assessment of the motor performance and functional ability in standing, walking, running and jumping.<sup>32</sup> GMFM is considered the primary outcome measure, as this has been examined widely in paediatric population and can be affected positively after a therapeutic intervention. The change from pre to 4-week post of GMDF-D will be used as the primary endpoint for calculating the effect size, as this measure is more likely to be mostly affected.<sup>33</sup>

### Secondary outcomes

- ▶ The Pediatric Balance Scale, score ranging 0–56 (higher score indicates better balance), for assessment of the functional balance skills.<sup>34</sup>
- ▶ The 10-meter walk test (10MWT) for assessment of gait's self selected low and high speed over ground and determination of the individualised training speeds over the treadmill, will be expressed as meters/second (m/s).<sup>35–37</sup>
- ▶ The timed up and go test for assessment of the dynamic balance control, will be expressed in seconds (s).<sup>38</sup>

**Table 1** Participant's timeline

Time point (period)	Enrolment	Allocation-baseline	4-week period of intervention or	4-week period of usual therapy	4-week post period	2-month post period
<b>Visit number (days)</b>	1 day	1–2 days	20 days	4–12 days	1–2 days	1–2 days
<b>Enrolment</b>						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
<b>Groups</b>						
FPBWSTT group			X			
Control group				X		
<b>Assessments</b>						
Primary outcomes		X			X	X
Secondary outcomes		X			X	X
Other prespecified outcomes		X				

FPBWSTT, functional partial body weight support treadmill training.

- ▶ The 6-minute walk test for assessment of physical condition and endurance, will be expressed in meters (m).<sup>39</sup>
- ▶ SARA applied in the Greek version for assessment of ataxia features, score range 0–40 (higher score indicates more severe ataxia).<sup>6,40</sup>
- ▶ Three-dimensional kinematic and kinetic analysis of lower limbs through motion and gait analysis applied with electronic recording of kinematics elements for the pelvis, hip, knee and foot of both lower limbs in the three planes of motion (sagittal, frontal and transverse). Since laterality severity does not occur in ataxia, each participant's dominant ankle power absorption and generation, expressed as Watt/kilogram will be collected for kinetic variable. Similarly, the dominant lower limb's mean gait deviations during (1) pelvis movement in all three planes of motion, (2) hip, knee and ankle movement in sagittal plane and (3) foot progression will be collected and expressed as normally disturbed data, quoted as normal SDs through Gait Deviation Index analysis (GDI).<sup>41</sup> The data recording and collection will be obtained by the Gait and Motion Analysis Lab of ELEPAP of Athens.
- ▶ Analysis of spatiotemporal gait features through 2 min recording over the treadmill with partial body weight support in the personalised low walking speed (75% of each participant's self-selected walking speed based on the 10MWT over ground). GaitSens software, incorporated in the LiteGait equipment will be used for recording and collecting the gait parameters. The dominant's lower limb step length, stride length and width length will be expressed in terms of meters (m), while step and stride time will be expressed in seconds (s).

### Sample size calculation

The design and analysis of this study has insufficient reference in order to identify with accuracy the sample size estimation. However, we used findings from a recent pilot study on adolescents with ataxia secondary to acquired brain injury and estimated the primary endpoint of GMFM-D domain from baseline to the end of the 4-week intervention period.<sup>12</sup> It was calculated that a sample size of 13 participants per group is required in order to have an 80% probability of demonstrating a difference between groups of >3% in % change from baseline to first month of GMFM-D (control: 2%±3, intervention: 5%±3) with a significance of 5% (two-tailed test). Sample size estimation was performed using G\*Power V.3.1.9.2 programme. In order to verify the above estimation, when the collection of five children per group is completed, the comparison of primary endpoint between groups will be performed and using the results of the analysis, sample size estimation will be made to determine the final number of the study sample, as this strategy has been suggested by a relevant review on sample size estimation approaches.<sup>42</sup>

### Clinical relevance

According to a recent study on comparison of distribution-based approaches for identifying a minimum clinically important difference for GMFM in paediatric gait disorders after a 4-week robotic assisted gait training, it seems that a benchmark of improvement in GMFM-D ranges between 0.8% and 5.2% for acute CP population.<sup>33</sup> We hypothesise that such range improvement could be a clinically meaningful change for the paediatric population with ataxia.

### Equipment

Gait training will be performed using a Lite Gait LGI 200P system accompanied by a Gait Keeper Treadmill system with a low start walking speed (0.1 km/hour) and built-in sensors for recording and collecting spatiotemporal gait data, through Gait Sens 2000 software. BiSym software, incorporated into LiteGait will be used for monitoring the percentage of partial body weight support, in standing position, during the application of tightening the overhead straps of the LiteGait with the buckles of the participant's harness. Two tablets connected with GaitSens and BiSym software, respectively will be used for displaying, monitoring and exporting the collected data. A harness and a groin piece will be used for obtaining the body weight support of the participant during standing, while FreeDome Yoke will be used as an accessory, as described in [table 2](#).

Gait and posture biomechanical data, collected by the Gait and Motion Analysis of ELEPAP of Athens will be processed with the Plug-in-Gait component for Workstation software (Vicon, Oxford, UK). Two force plates (AMTI) in the middle portion of a 10-metre walkway will be used to capture force plate data from five gait trials sequentially in each participant's self-selected barefoot cadence independently or with assistance, according to each participant's GMFCS level. The data will be acquired by 10 Vicon Cameras (6MXT10 and 4 Verov2.2) at 100 Hz and 2 Basler (Pentaxlenses) digital video cameras 50 Hz. Vicon Nexus V.2.9.1 recording software for the 16 passive reflective markers gap-filling and data filtering will be used. Further processing and extraction of data will be made through Vicon Polygon V.3.5.1 software.

The anatomical key points for the attached 16 reflective markers are in accordance with the standardised Plug-in-Gait biomechanical analysis model for the pelvis and the lower limbs (the anterior and posterior iliac crest spine, the middle of the lateral border of the femur, the lateral femoral condyle, the middle of the fibula, the lateral malleolus, the calcaneus and in between the heads of the second and third metatarsus).

Valid force plate data will be available from five left and five right gait cycles, identified as having valid kinematic and kinetic data (whole foot landing in the force plate) for each participant. The trial's valid data which are closest to the mean of the overall valid gait trials will be used for statistical analysis.

**Table 2** Description of the functional activities and the recording of motor performance

Functional activities	Description	Motor performance
1. Changing direction	The participant is asked to change direction every 30 s in sideways to right, to left and backwards, following the same order. For this activity, participants' harness is buckled with the FreeDome Yoke accessory of LiteGait	Record of synchronised steps in every direction
2. Throwing and catching a ball	The participant is asked to catch and throw back a ball of 15 cm diameter to the physiotherapist who is in front of him/her in a distance of 1.5 m	Record of succeeded catching and throwing of the ball over a maximum total number of 50 efforts
3. Crossing obstacles	The participant is asked to step subsequently over obstacles (2.5 cm height/7 cm width and length). Obstacles are placed by the physiotherapist in front of each foot for approximately 2.5 min in each, in a maximum of 30 efforts	Record of succeeded stepping over obstacles in each foot in a maximum of 30 efforts in each foot
4. Walking in a straight line	The participant is asked to walk in a white straight line located in the middle of the belt of the treadmill, while his hands are stretched upright (180° of shoulder flexion) holding the Yoke of the LiteGait, in order to stabilise and avoid the excessive trunk transfer in every step	Recording of the continuous steps on the straight line
5. Target demonstration	The participant is asked to hold a marker and target as precise as possible numbers from 1 to 15 in 2 cm <sup>2</sup> , located in a board in front of him/her, in a distance at about 50% of participant's arm reach. The task will last for 2.5 min for each arm	Record of targeted succeeded demonstrations and record of the deviation in cm of the misplaced efforts
6. Holding a ball on a glass	The participant is asked to hold a glass of 8 cm height and maintain the ball of 8 cm diameter, located on the nozzle of the glass of 7.5 cm diameter. The task will last for 2.5 min for each arm	Record of the efforts and the time of holding the ball, without falling

### Assessors

Assessment will be undertaken by the same physiotherapy team, experienced in the management of paediatric patients. All assessors involved in data collection are trained in study procedures and familiar with the use of the study instruments and measurements.

Blind assessors will be those involved in kinetic and kinematic lower limb gait analysis, obtained by the Gait and Motion Analysis Lab of ELEPAP of Athens.

### Intervention description

The suggested protocol is based on the application of a speed interval treadmill protocol with functional dual tasking modifications, resulting from literature findings.<sup>21–23 35</sup> All phases will be administered with partial body weight support. Support will be at <40% of each participant's body weight, as the literature suggests in order to improve performance of gait in different kind of population with gait impairments.<sup>43 44</sup> Twenty sessions of 45 min each will be completed for a 4-week intensive programme period (5 days a week). The 45 min period will consist of two phases during which participants will wear their shoes with any insoles they may use:

*Phase 1: Walking training on the treadmill.* This phase will consist of 30 min walking on the treadmill with a <40% body weight support, according to the recording of body weight percentage by BiSym software. The treadmill speed will be set to the individualised low and high speed of each participant which will be alternated every 30 s. Both low and high speed will be personalised and will be formed by 75% of the respective self-selected and fast velocity speeds over ground, according to the 10 m walking test. The high speed will be gradually increased per session up to 5% of the set maximum speed achieved the previous day. At each change of speed, the child will be informed by the physiotherapist, in order to properly

adjust his/her gait and will be encouraged verbally and visually to improve the gait pattern. Application of facilitation manipulations is allowed to a minimum in order to enhance the improvement of the child's gait. In the 30 min of gait training there will be short breaks, whenever needed during which the child will stand upright in a physical position. The goal is to achieve a total of 20 min of walking. The handles will not be used throughout the gait training to enhance the reciprocal arm swing as much as possible.

*Phase 2: Functional activities—dual task.* Dual motor functional training will last 15 min. In this phase, functional exercises will be performed during the individualised constant low walking speed on the treadmill (table 2). In each session, three of the six activities will be applied in a rotating cycle, as shown in table 3, each of which will last 5 min. In each session, the performance of each participant will be recorded and the physiotherapist will encourage the gradual improvement of the motor performance in each activity with verbal and visual guidance.

### Usual/typical care

Participants both in the EG and CG will continue receiving their usual typical care, formed by physiotherapy and any

**Table 3** Cyclic training of functional activities during the 20 days of session

Days	Functional activities
1, 6, 11 and 16 days	1, 2, 3
2, 7, 12 and 17 days	2, 3, 4
3, 8, 13 and 18 days	3, 4, 5
4, 9, 14 and 19 days	4, 5, 6
5, 10, 15 and 20 days	5, 6, 1

other form of therapy that the child requires, such as occupational therapy, speech therapy etc. It is anticipated that typical physiotherapy (alongside with hydrotherapy or horse riding) will constitute only of 1–3 days per week sessions, otherwise it can be considered as an intensive physiotherapy programme.<sup>45 46</sup>

### Statistical analysis plan

Data will be expressed as mean±SD or median (IQR), in case of violation of normality, for continuous variables and as frequencies, percentages for categorical variables. The Kolmogorov-Smirnov test will be used for normality analysis of the parameters. Homogeneity between groups will be performed using independent samples t-test and Fisher's exact test.

Two-way mixed ANOVA model will examine the interaction between the 'intervention' and 'time' factors. The comparison of raw data variables at each time point between groups will be performed using the above model.

One factor repeated measures ANOVA model will be used for the comparison of different time measurement of variables for each group, in order to estimate the variation of time measurements in each group, during the intervention period. Pairwise multiple comparisons will be examined using the Bonferroni test. Friedman and Wilcoxon test will be used in case of violation of normality. The efficacy of the intervention during the observation period will be evaluated by calculating the mean percentage changes from baseline after 1 and 3 months, respectively. Comparison of percentage change from baseline to each time point of parameters between interventions will be analysed using the independent samples t-test or Mann-Whitney in case of violation of normality. If there is not homogeneity between interventions in relation to demographic or clinical characteristics, ANCOVA model will be used for the analysis of variables using as covariates the above characteristics which differentiate the compared group. Potential missing values from non-adherence or possible deviations from the per protocol assignment will be discussed and analysed through intention to treat analysis. Multiple imputation will be used for missing value analysis.<sup>47</sup>

All tests are two-sided, statistical significance will be set at  $p < 0.05$ . All analyses will be carried out using the statistical package SPSS V.21.00 (IBM Corporation).

### Data collection, management and monitoring

All relevant information is provided in online supplemental material 1 (S3.10–S3.15).

### Ethics and dissemination

The clinical trial will be conducted in compliance with this study protocol, the Declaration of Helsinki and Good Clinical Practice. Ethical Approval has been obtained by the Ethics Committee of the University of West Attica (study's protocol: 14η/26-04-2021) and the 'ATTIKON' General University Hospital of Athens (study's protocol: Γ ΠΑΙΔ, ΕΒΔ 149/20-3-2020). This study will be reported

in accordance with the Consolidated Standards of Reporting Trials 2010 statement.

Dissemination to each participant's personal findings will be obtained with the end of the research study. Dissemination of the findings to different interest groups as well as participants or other children with ataxia and/or their parents/carers will be made through journal papers and/or conference presentations. Trial results of the main trial will be submitted for publication in a peer-reviewed journal.

**Twitter** Alexandra Lepoura @ALepoura

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### ORCID iD

Alexandra Lepoura <http://orcid.org/0000-0002-3353-0388>

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