Study Protocol

Formal study title: The role of vibration therapy in improving the health and mobility of young children with cerebral palsy.

Short study title: Vibration therapy for children with cerebral palsy

Lead Investigator: Professor Paul Hofman, Dr Silmara Gusso

Co-ordinating Investigator: PhD student Alena Adaikina

I. Project overview

Cerebral palsy (CP) is the most common disability in childhood with an estimated prevalence of 2 per 1,000 children [1, 2]. One of the main characteristics of CP is a reduction in mobility. The key factors contributing to changes in mobility are muscle weakness and spasticity [3, 4]. There are a number of therapeutic interventions aimed at improving muscle weakness and spasticity and consequently mobility in CP patients. These include orthopaedic surgery, antispastic drug therapy, exercise rehabilitation, and occupational therapy [5, 6]. However, these interventions have limitations, including high cost, complexity, and the need for specialized equipment and/or professional staff [7-9]. Children with CP tend to be less physically active than their non-CP peers [10]. Therefore, there is a need for therapies that are effective and cost efficient in improving mobility and muscle strength in this population. Vibration therapy (VT) has the potential to fill this gap and be incorporated into the routine care of children with CP [11, 12]. A recent study by our group showed a positive impact of VT on mobility, muscle mass, muscle function as well as bone health in 40 adolescents with CP [13]. Twenty weeks of VT increased mobility by 11 % in those adolescents with mild CP ($p = 0.0001$) and by 35 % on those with moderate CP ($p < 0.0001$). Lean mass increased at the total body level (+ 2.1%; $p = 0.0003$), in the trunk (+ 2.4%; $p = 0.004$), and in the lower limbs (+ 2.2%; $p = 0.012$). Bone mineral density also increased in total body (+ 0.8%; $p = 0.013$), lumbar spine (+ 1.3%; $p = 0.003$), and lower limbs (+ 2.2%; $p < 0.0001$). The positive effect of VT was also reported on muscle function: the time of chair rising test (independent standing up from the sitting position) reduced by 1.5 seconds ($p = 0.0004$) [13].

We anticipate that younger children will benefit similarly or more due to their extensive growth and development period, as the level of mobility and physical fitness play an important role in achieving an optimal level of development [14-16]. The current literature is sparse and has heterogeneous methodological data, with protocols varying in intensity, length and equipment used, making the interpretation of results difficult [12, 14, 16-22]. To our knowledge, this study is the first study to examine the effects of two vibration therapy intensity protocols on mobility, muscle and bone health, as well as respiratory function in young children ages 5-12 with CP.

II. Outcome measures

The primary outcome measure is:

- Mobility as assessed by the 6-minute walk test

The secondary outcome measures are:

- Body composition assessed by Dual Energy X-Ray Absorptiometry
- Gross motor function assessed by Gross motor function measure, dimension D and E
- Muscle function assessed by jump power using the Leonardo Mechanography force plate
- Balance assessed by the Leonardo Mechanography force plate
- Muscle strength assessed by hand-held dynamometer
- Respiratory function assessed by a portable spirometer
- Physical Activity assessed by using Physical Activity Monitor
- Quality of life questionnaire assessed by the Cerebral Palsy Quality of Life Questionnaire for Primary Caregiver

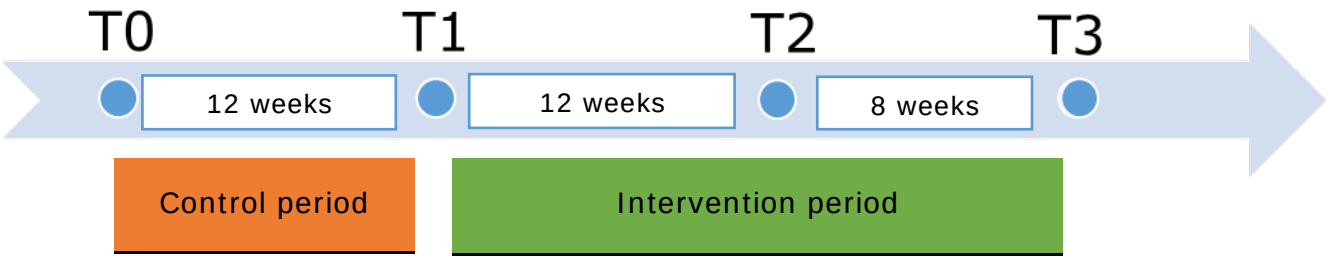
III. Study design

The research project is designed as a randomized clinical study, where all participants will act as their own control having 12 weeks period lead on prior to the intervention. For the intervention part of the study, participants will be randomized into two different groups varying in the frequency of the vibration therapy (VT) (20 Hz and 25 Hz).

All participants will be assessed 4 times over a period of 8 months: T0 - baseline, T1 - 12 weeks after the lead on period (control), T2 – after 12 weeks of vibration therapy, T3 – after completing 20 weeks of vibration therapy.

During the control period (T0 – T1), participants will continue their usual activity levels and standard care.

The intervention period for all participants will last for 20 weeks.



IV. Sample calculation

The sample calculation was performed in GPower software version 3.1.9.2. For the calculation, we used the mean and standard deviation obtained in the 6MWT from the clinical trial performed of 40 participants with cerebral palsy [1]. Adopting an alpha 0.05 and a power of 0.95, a minimum of 44 participants for two groups was found. Considering a 10% drop-out rate the final sample consisted of 48 participants overall with 24 for each intervention group.

V. Recruitment process

The study aims to recruit 48 children to allow for no shows and drop-offs. Recruitment will be conducted using the pediatric neurology and developmental database held by the Auckland District Health Board (ADHB). Researchers will identify prospective participants from the database using the exclusion/ inclusion criteria described below as search variables. Those who fit the study criteria will initially be approached by the pediatricians or nurses during their clinic visit. Potential participants will also be identified at their regular pediatric neurology clinic visits. School physiotherapists at satellite schools (Auckland area) will also be informed of the study and will be able to contact researchers if their school students/ families are interested in participating.

Once potential participants are identified a phone call will be made to parents/ caregivers to provide more information about the study. An information package about the study will then be sent by email or mail. This package will include the participant information sheet and consent forms.

Two-five days after the package is sent, researchers will contact prospective families to answer any questions and if possible confirm or not their participation in the study.

Informed Consent

Participants and their parents/legal guardians will be provided with a participant information sheet (PIS), consent form (CF) and accent form (AF) for children.

Written consent will be obtained from all parents/guardians before the first assessment. Oral/ written assent will be obtained from the participating child when possible.

VI. Participants

Prospective participants aged 5-12 years with cerebral palsy (GMFCS I-III) will be recruited from the ADHB pediatric neurology and developmental database from the Auckland area.

Inclusion criteria:

1. Male or female, aged between 5 years 0 months and 12 years 11 months
2. Have diagnosed cerebral palsy with GMFCS I - III
3. Be able to safely stand on the vibration platform
4. Be able to understand the researcher's instructions and follow them

5. Have informed consent by parent/guardian with participant assent

6. An absence of planned surgery for the next 8 months

Exclusion criteria:

1. A bone fracture within 12 weeks of enrolment
2. Acute thrombosis, tendinitis, nephrolithiasis, discopathy or arthritis
3. History of clinically significant organic disease or findings on physical examination, which in the opinion of the Investigator would prevent the patient from completing the study.
4. History of using any of the following medications, regardless of dose, for at least 1 month, within 3 months of enrolment: anabolic agents, glucocorticoids (does not include inhaled glucocorticoids) or growth hormone.
5. History of botulinum toxin injection into lower limbs within 3 months of enrollment

Randomization

Randomization will be done immediately after the initial assessment using an online random number generator available at https://www.random.org/. Participants will be allocated to group 1 (VT intensity 20 Hz) and group 2 (VT intensity 25 Hz)

VII. Assessment

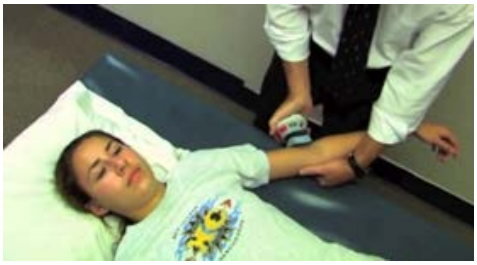
All participants will undergo 4 assessment visits at the Liggins Institute, University of Auckland (85 Park Rd Grafton Auckland): visit 1 – Baseline (T0); visit 2 - after 12 weeks of the lead on period (control period) (T1); visit 3 – after 12 weeks of vibration therapy (T2); visit 4 – after completing 20 weeks of vibration therapy (T3).

Each assessment visit will take approximately two hours. All assessments are internationally recognized and have been used in a similar population.

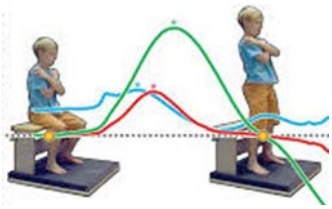
Assessment visits (T0-T3) will comprehend the following tests:

1. **Basic measurements**
   - ***Height*** will be measured using a Harpenden stadiometer. Measurements will be done 3 times and the average out of three will be recorded.
   - ***Weight*** will be measured on the Wedderburn VM206 scale without shoes and outerwear (when possible)
   - ***Blood pressure***, ***heart rate, and oxygen saturation*** will be measured in a sitting position after 10 min of rest prior to the start of functional tests. We will use a standard mercury sphygmomanometer with an appropriately-sized cuff on the non-dominant arm to measure blood pressure and a finger sensor to record oxygen saturation (Dinamap ProCare 100, GE Healthcare, Freiburg, Germany).

2. Muscle function



- ***Muscle strength*** will be assessed using hand-held dynamometer (MicroFET2) to measure the force generated by a muscle during 3 sec of isometric contraction. Lower limb muscles on both sides (left and right) will be tested 3 times, with the highest strength value used for statistical analysis. Muscle tests will include:
    - Hip flexion and extension
    - Knee flexion and extension
    - Hip abduction
    - Ankle dorsiflexion
- ***Muscle power and balance*** will be assessed using the Leonardo Mechanography Ground Reaction Force Plate (Novotec Medical, Pforzheim, Germany). Assessments will include:
    - Chair rising test. The test is performed with a specially-designed seat (Novotec Medical) placed on the plate, with participants standing up and sitting down 5 times in a row as fast as possible without hand assistance. The test will be done three times with the best result is recorded. For analysis, the total time to complete the test (T_{total}), maximum force ($F_{max\ tot}$) and power (P_{max}) in both legs will be used.



    - Single two-leg jump test. The child will be instructed to jump as high as possible using both legs and landing on the forefoot. The test will be done three times after one practice with the best result is recorded. Variables of interest include the maximal jump height ($2LJ_h$), maximal total power per body weight ($P_{max\ tot}$), maximal total force ($F_{max\ tot}$), maximal velocity (2LJv) and the Esslinger Fitness Index (EFI).

    - Balance test. A participant will be instructed to stand still for 10 seconds on three different positions: on both legs, on the right leg, and on the left leg. For those kids who are not stable, we will use hand assistance with a recording that in their notes and using assistance in all subsequent balance tests. The best result out of three trials will be recorded. The outcome parameter of the test is the standard ellipse area (StdEA).

3. Physical function

- 6-minute walk test. Participants will be asked to walk as fast as possible between 2 cones separated by 25m along a long, flat, straight, indoor corridor for exactly 6 minutes [2]. The total distance covered and the time taken to reach individual milestones (25m) will be recorded. We will use the Rated Perceived Exertion (RPE) Scale to measure overall fatigue

before and after the test. The test will be performed with shoes on; children may use their walking aid to complete the test (but not a wheelchair). Participants will be able to stop and rest if necessary, and then continue walking until the 6 minutes are completed. This test has been shown to be a reliable and valid test in children with cerebral palsy [3].

- 10 meters walk/run test. The time to cover 10meters will be recorded according to the 10meter walk/run test specifications and walking speed will be calculated. Children are permitted to walk if unable to run [4]. The test will be done three times; the best time will be taken for the statistical analysis.

4. **Gross motor function measure (GMFM)** is a clinical tool designed to evaluate changes in gross motor function in children with cerebral palsy. Dimension D (standing) and E (walking, running, jumping) will be assessed. Participants will be tested performing different tasks according to 4-point scale, where 0 point means a child does not initiate a movement of the task; 1 – a child initiates a task; 2- the test is partially completed; 3 – the test is completed.

5. **Respiratory function** will be tested using a spirometer CareFusion MicroLab MK8. The test involves taking a full breath in and blowing out with the maximum effort into a tube attached to the spirometer machine. Measures will include forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and ratio FEV1/FVC. Three attempts will be performed with the best result taken for statistical analysis.

6. **Bone Density and Body Composition.**

   - ***Whole-body dual-energy X-ray absorptiometry (DXA),*** (Lunar Prodigy 2000, General Electric, Madison, WI, USA) will be used to determine lean mass, fat free mass, fat mass, body mass, bone mineral density, and bone mineral content. Participants will be requested to lie still on a table for approximately 5 min for each scan. We will use a wrapping technique when required to prevent movements. During the scan, a large scanning arm will pass over the body to take a series of X-ray images. We will perform two scans: the whole body and lumbar spine. DEXA scans use small radiation doses (0.03ms) which are comparable to the natural background radiation for 1 day as compared to that by 10 days for standard X-ray. There is an international consensus that DEXA scans do not constitute a safety concern for children and adolescents.

   - The previous bone fractures information will be collected from the participant's medical records.

7. **Quality of life**

   Parents/caregivers will be asked to complete the Cerebral Palsy Quality of Life Questionnaire for Primary Caregiver (CP QOL) to evaluate child well-being, physical activities, daily activity life, communication and social well-being [5]. The questionnaire consists of 66 items. Approximately 15-25

min is required to complete the questionnaire by an adult. It is expected parents/caregivers will fill the questionnaire during assessment sessions.

8. Physical Activity

Participants will wear a physical activity monitor (ActivPAL™) for 5 days following their assessment [6, 7]. ActivPAL™ records the information on how much time a child spent sitting, lying, and walking during the day [6]. The device is extremely lightweight (15 grams) and unobtrusive. The ActivPAL™ will be waterproofed by wrapping with a medical grade adhesive covering (e.g. 3M Tegaderm or S&N Opsite flexifix) and attached to the front of the non-dominant thigh with a sheet of hypoallergenic dressing, such as Hypafix. This attachment provides up to 5 days continuous wear, allowing the wearer to shower without removing the ActivPAL™. At the end of each assessment visit the ActivPAL™ will be applied and participants will be given clear written instructions on how to correctly use the device and replace it in case it should be done (for example, in case of skin irritation). The research team will also follow up with families via phone or email (the parents preferred method) at least once during the following 5 days to ensure there are no concerns or issues with the device being used.

Diaries:

- ***Falls diary*.** Participants and their parents will be asked to complete a Falls diary where they note down any falls children have and injuries sustained from the fall during their study participation.
- ***Vibration therapy diary*.** Participants will be asked to record their training sessions and any symptoms they experience during the 20 weeks of vibration training. Participants will be asked to maintain a training diary to monitor compliance. Data recorded will include the date, intensity, and duration of training, as well as any comments regarding adverse events, tiredness, or pain.

VIII. Intervention period

Vibration therapy will be performed using the Galileo Basic vibration plates (Novotec Medical, Pforzheim, Germany). Each session will last 18 min: 3 min vibration followed by 3 minutes rest- repeated 3 times. Sessions will be performed 4 times a week, over a 20-week period. Participants will start with sessions of three 1-minute bouts at 12 Hz, and both intensity and duration will be gradually increased according to the response of each individual. Each intervention group will have its own target intensity: either 20 or 25 Hz. By the end of week 4, all participants should be training at the prescribed protocol of 3 sets of 3 minutes at their target intensity. Training intensity will be maintained at 20 or 25 Hz depending on the intervention group for the remainder of the intervention period.

Participants will stand barefoot on the plate with knees slightly bent. An adjustable metal frame will be used for participants with poor balance for safely. Training sessions will be performed at home or at school. An exercise

physiologist (PhD candidate) from the research team will supervise the participants performing training at home once a week and all 4 days of the week for those doing it at school, in order to monitor progress and provide feedback/support. Parents/caregivers will provide ongoing supervision of home sessions.

IX. Safety monitoring process

To monitor safety, the study's internal safety monitoring committee has been created. The committee will have meetings on a quarterly basis. In case of a serious adverse event (s), the committee will have meetings more frequently.

The study safety monitoring committee consists of:

- Alena Adaikina, Coordinating Investigator, PhD student, Liggins Institute, The University of Auckland
- Prof Paul Hofman, Co-investigator, Paediatric Endocrinologist, Liggins Institute, The University of Auckland
- Dr Silmara Gusso, Co-investigator, Senior Lecturer, Department of Exercise Sciences, The University of Auckland
- Prof Craig Munns, Professor of Paediatric Bone and Mineral Medicine, Medical School University of Sydney, Australia

Alena Adaikina will be the primary point of contact for all families and physiotherapists. Continued communication with patients/families during the intervention period will assist in identifying adverse events. Participants and their families will be asked to record and immediately report any adverse events that may be associated with VT, including tiredness or pain. All adverse events will be reported by Alena Adaikina to the safety monitoring committee to discuss.

<u>Patient safety narrative will describe the following:</u>

- The nature, intensity, and outcome of the event
- The circumstances leading to the event
- Treatment or intervention
- The action is taken with the study

<u>Vibration therapy will be discontinued in any participant who:</u>

- Experiences excessive or persistent pain/aching;
- Experiences bone fractures or any illness that would preclude training.

<u>The study will be terminated if:</u>

- Two serious adverse events of the same nature will be registered.

In the case of premature termination of the trial, the research team will inform the ethics committee and the sponsor in writing with stated reasons for termination.

REFERENCES:

1. Gusso, S., et al., *Effects of whole-body vibration training on physical function, bone and muscle mass in adolescents and young adults with cerebral palsy.* Scientific Reports, 2016. **6**.
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7. Ishikawa, S., et al., *Reliably Measuring Ambulatory Activity Levels of Children and Adolescents With Cerebral Palsy.* Archives of Physical Medicine and Rehabilitation, 2013. **94**(1): p. 132-137.