**Do interventions targeting proprioceptive feedback and exercise improve functional gait and reduce falls and falls risk in people with multiple sclerosis?**

**Interventions to improve gait and reduce falls in people with MS**

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# STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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PROTOCOL SYNOPSIS

|  |  |
| --- | --- |
| Title | **Do interventions targeting proprioceptive feedback and exercise improve functional gait and reduce falls and falls risk in people with multiple sclerosis?** |
| Objectives | **Primary: The aims of this project are to determine the effectiveness of an exercise protocol with increased proprioceptive feedback via whole-body vibration to reduce prospective falls and falls risk compared to a protocol of the same duration and intensity of standard exercises in people with multiple sclerosis.**  **Secondary: To determine the effectiveness of a home­based whole­body vibration protocol to improve mobility and functional gait outcomes in people with MS.** |
| Study Design | **This is a prospective, parallel­group, pretest­posttest, single­blind, randomised controlled study** |
| Planned Sample Size | **100 subjects (age 18-65) will be recruited for this study.** |
| Selection Criteria | **Participants with MS who can walk independently (with or without the use of an assistive device) will be invited to participate. Participants will be screened and excluded from the study if they have had a relapse within the last 3 months, corticosteroid treatment within 28 days of the study commencement, or have contra­indications for exercise.** |
| Study Procedures | **Participants will be randomly allocated to two groups. Both groups will receive the same home­based exercise program. The whole-body vibration group will perform the exercises on a whole­body vibration platform, whereas the control group will perform the *same* exercises on the ground. Outcome measures will be assessed by a blinded assessor and recorded at baseline and at the end of the intervention (week 10) except prospective falls, which will be monitored for 20 weeks.** |
| Statistical Procedures  Sample Size Calculation:  Analysis Plan: | **Between group comparisons will be made using General Linear Models (ANCOVA). Negative Binomial Regression will be used for Falls data. Change scores (pre minus post) and effect sizes will be calculated. The sample size of 50 per group was selected based on the recent findings of Uszynski and colleagues (7).** |
| Duration of the study | **3 years** |

# GLOSSARY OF ABBREVIATIONS

|  |  |
| --- | --- |
| **ABBREVIATION** | **TERM** |
| MS | Multiple sclerosis |
| WBV | Whole-body vibration |
|  |  |

# Study Management

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* 1. **Statistician**

NA

* 1. **Internal Trial Committees**

NA

* 1. **Independent Safety and Data Monitoring Committee**

NA

* 1. **Sponsor**

University of Sydney

* 1. **Funding and resources**

This study is funded from an incubator grant from MS Research Australia

# INTRODUCTION AND BACKGROUND

* 1. **Background Information**

Fatigue, weakness, and sensory problems are common signs and symptoms reported by people with multiple sclerosis (MS). Importantly, people with MS report loss of mobility as their greatest concern (3). The loss of mobility is often related to fatigue and weakness. However, little attention has been directed at sensory impairments. Feedback from sensory afferents, particularly muscle spindles, provides critical proprioceptive information for normal motor control. Proprioception is the knowledge of the body which allows us to respond to the environment around us and react rapidly in changing circumstances. Deficits in proprioceptive feedback can be measured as decreased reaction time, movement detection, and impaired position sense all of which can lead to reduced walking speed and impaired balance. These measures are associated with increased risk of falls and thus, fear avoidance behaviour and loss of mobility (5, 9).

**Research Question**

Do interventions of exercise training that incorporate additional proprioceptive sensory feedback improve mobility and functional gait outcomes and reduce prospective falls and/or falls risk in people with multiple sclerosis?

* 1. **Rationale for Current Study**

Maintaining safe mobility is a key issue for people with MS (3). Up to 30% of people with MS will have multiple falls (≥ 3) in the next 6 months (3). Multiple fallers in studies of older people have been identified using the Physiological Profile Assessment (PPA) scores with accuracies up to 75% (9). A PPA score of >2 would indicate a high risk of falling and would be classified as a multiple faller in older people (5, 9), as well as in people with MS (Hoang et al, unpublished data).

A range of neuropsychological, physical, and functional mobility impairments contribute to the multifactoral causes for falls (5). Fatigue, weakness, balance impairments, altered gait patterns, and fear of falling are common. Sensory impairments are also common, although this has received little attention. Interventions designed to improve feedback from sensory afferents may act to improve motor control, balance, and gait and thus, improve mobility and decrease falls or reduce falls risk.

Whole-body vibration (WBV) is a technology that is thought to stimulate sensory afferent input to the motoneurones and thus, enhance muscle output and motor control (6). While most studies investigating the use of WBV in people with MS are pilot in nature or significantly under-powered, previous reports showed some evidence that WBV exercise interventions lasting at least 3 weeks could improve measures in the Timed Up and Go Test, the 6 Minute Walk Test, and the 10 meter Walk Test (2,5,7). A systematic review reported that there is minor evidence from the studies with the best methodological quality that the long-term effects of WBV can improve strength, proprioception, gait, and balance (6). This suggests WBV can reduce fall risk and possibly reduce prospective falls. However, of the limited number of studies using WBV, none have examined falls or fall risk. Hence, this project will determine the effectiveness of WBV on previously measured mobility outcomes, but more importantly falls risk and prospective falls.

# STUDY OBJECTIVES

* 1. **Primary Objective**

The aim of this project is to determine the effectiveness of an exercise protocol with increased proprioceptive feed back via whole-body vibration to reduce prospective falls and falls risk compared to a protocol of the same duration and intensity of standard exercises in people with multiple sclerosis.

**Primary outcome measures include**

1. Number of prospective falls compared to standard exercises.
2. Falls risk scores as measured with the Physiological Profile Assessment (PPA) short form
   1. **Secondary Objectives**

To determine the effectiveness of a home­based whole­body vibration protocol to improve mobility and functional gait outcomes in people with MS .

**Secondary outcome measures include**

1. Dynamic balance as measured by the Timed Up and Go Test and the choice stepping reaction time test.
2. Endurance as measured by the 6 Minute Walk Test
3. Functional mobility as measured by the multiple sclerosis functional composite score which is comprised of the symbol-digit test, 9-Hole Peg test, and the 10‑meter walk test.

# STUDY DESIGN

* 1. **Type of Study**

This study is a randomised, single blind control trial using a pre-post intervention design targeting proprioceptive feedback and exercise training to improve functional gait and reduce falls and falls risk in people with multiple sclerosis.

* 1. **Study Design**

Assessments will occur at the University of Sydney Cumberland campus and Neuroscience Research Australia. The intervention program will occur in the participant’s home.

*Research Design*

To determine the effectiveness of a home-based whole-body vibration protocol to improve mobility outcomes and reduce prospective falls and/or falls risk a prospective, parallel-group, pretest-posttest, single-blind, randomised controlled study will be conducted. In addition, reliability of three assessment measures, the choice stepping reaction time test, the physiological profile assessment, and the multiple sclerosis functional composite score will be assessed.

100 subjects (age 18-65) will be randomly allocated to two groups, a control group and an intervention group (WBV group). Randomisation to intervention or control groups will occur after completion of the baseline assessments. Permuted block randomisation of 6-10 will be performed using web-based randomisation software (i.e., a concealed randomisation system). Both groups will receive the same home-based exercise program. The WBV group will perform the exercises on a whole-body vibration platform, whereas the control group will perform the *same* exercises on the ground. Over one year, five intervention blocks lasting 10 weeks will be delivered. 20 participants will be recruited for each block, 10 of which will receive a WBV platform delivered to their home. At the conclusion of the 10-week intervention block, the next 20 participants will begin the second 10-week block. This will be repeated three additional times (10-week intervention blocks 3, 4, and 5) bringing the total number of participants in each group to 50 at the end of one year. To examine reliability for the choice stepping reaction time test, the physiological profile assessment, and the multiple sclerosis functional composite score, 50 participants with Expanded Disability Status Scale (EDSS) Levels ranging from 2-6 (n=10 for each of the five levels for a total of 50 participants) will return 1 week after the initial evaluation to be reassessed using the same testing protocol.

*Participant selection*

Participants with MS who can walk independently (with or without the use of an assistive device) will be invited to participate. Participants will be screened and excluded from the study if they have had a relapse within the last 3 months, corticosteroid treatment within 28 days of the study commencement, or have contra-indications for exercise.

*Assessment measures*

Outcome measures will be assessed by a blinded assessor and recorded at baseline and at the end of the intervention (week 10) except prospective falls, which will be monitored for 20 weeks (see below). In addition, 50 subjects will be invited to participate in a second assessment 1 week after the initial assessment to establish reliability for the outcome measures. Outcome measures for each of the five hypotheses are listed below.

1. The primary outcome measures are prospective falls and falls risk. Prospective falls will be measured over 20 weeks by the use of ~monthly falls diaries to be returned to the investigators each month, with monthly telephone follow-up (i.e. falls during the 10 weeks from baseline to the end of the intervention and then during the 10 weeks following the end of the intervention). A fall is defined as “unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure.”(2) Falls risk will be assessed using the Physiological Profile Assessment (PPA) fall risk index score. This is a series of tests composed of weighted values from five sensorimotor and balance domains: quadriceps muscle strength, hand reaction time, proprioception, postural sway, and visual contrast sensitivity. The PPA is a valid and reliable test for falls risk (5, 9).

Secondary mobility outcomes will be assessed as follows:

1. Dynamic balance will be assessed by the Timed Up and Go Test (TUG) and the choice stepping reaction time (CSRT). The TUG test is measured in seconds. It requires the participant to stand up from a chair, walk 3 meters, turn around, walk back and be seated. The Timed Up and Go Test has shown good reliability and concurrent validity in people with MS (7, 8). The CSRT requires participants to stand on a portable rubber mat and step quickly and accurately onto four targets for a total of 20 steps while being timed. The CSRT test has good validity and reliability in older people(1) and has been recently shown to have excellent validity in people with MS (4).

2. Endurance will be assessed by using the 6-minute Walk Test. This test requires participants to walk as quickly and safely as possible for 6 minutes on a 10-meter track. The total distance walked in 6 minutes is measured in meters. This test has been shown to be a valid and reliable measure in people with MS (7, 8).

3. The multiple sclerosis functional composite (MSFC) score. The MSFC consists of timed tests of walking, arm function, and cognitive function. The walking function is assessed using the 10-meter Walk Test. This test requires participants to walk independently across a linear 10-meter course as fast and safely as possible from a static start. This test has shown to be valid and reliable in people with MS (7, 8). The arm function component is measured using the 9-Hole Peg Test (9HPT) which consists of moving pegs from a box into holes on a peg-board then back again. The cognitive function is measured with the symbol-digit test (SDMT). This test requires participants to pair specific numbers with given geometric figures in 90 seconds. Taken together, the composite score of the MSFC correlates well with the Expanded Disability Status Scale (EDSS) used for people with MS, particularly for those at lower EDSS levels (10)

*Interventions*

Both groups will receive two supervised sessions by a trained research assistant (either a physiotherapist or exercise physiologist). The first session will occur after the initial assessment and the second halfway into the intervention block. Participants will be instructed by the research assistant in four exercises to be performed at home, at least three times a week for 10 weeks. Participants also receive phone calls every ~4 weeks by the research assistant to ensure compliance and appropriate progression. If participants (in either group) experience a relapse during participation they will be advised to stop exercise until after being reviewed by their physician and deemed ready to exercise again. The follow up measures for these participants will be conducted as their conditions allow. The Fall Calendars will be collected ~monthly for 20 weeks. The control group will be instructed to perform the exercises on a hard, stable surface. The WBV group will be instructed in the use of the SilverMink V-988 electrically controlled exercise system supplied WBV unit supplied by SaunaGem Australis and perform the exercises on the WBV platform. The SilverMink WBV system is registered with Australian Register of Therapeutic Goods (ARTG). The ARTG Number is 136007; the ARTG Product Number and Name: 222559 Massager, physical therapy. Halfway into the 10-week intervention block participants will receive an additional home visit for instructions in using a weighted vest to increase exercise progression as appropriate. The exercises selected are listed in Table 1 (See Attachment 3) and are adapted from Uszynski and colleagues (11). Potential benefits of using the WBV unit may be improved mobility capacity and a reduction to their risk of falls from our study. Potential risks using the unit include the possibility of falling off the platform, which could result in other injuries. However, the WBV platforms have handles that participants are able to hold onto and a safety strap to prevent them from falling backwards off the unit (see product information booklet).

* 1. **Number of Participants**

We will recruit 100 participants for this study.

* 1. **Study sites**

Assessments will occur at the University of Sydney Cumberland campus and Neuroscience Research Australia. The intervention program for will occur in the participant’s home.

* 1. **Expected Duration of Study**

This study will start January 2016 with recruitment of the first block of participants beginning their 10wk session once Ethical approval has been received. The earliest completion date will be March 2017, however the completion date may be extended until later in 2017 depending on recruitment rate.

* 1. **Primary and Secondary Outcome Measures**

The primary outcome measure is prospective falls over 20 weeks and/or falls risk. Secondary mobility outcomes are dynamic balance, endurance, and the MSFC.

Assessment of these outcomes is listed above in Section 4.2.

# PARTICIPANT ENROLLMENT AND RANDOMISATION

* 1. **Recruitment**

Participation will be via two “opt in” mechanisms. 1) Via assistance of health professionals invitations will be given to participants who attend routine physiotherapy assessments/exercises at MS Study Centre, Lidcombe NSW (MS Australia ACT/NSW/VIC). Potential participants will be provided with written information about the study with contact details of a research staff member to contact if they are interested in participating in the trial. 2) Invitations will be sent to participants who took part in our pilot study who provided consent to be contacted for future studies. 3) Information about the study with contact details of a research staff member will be made available at offices of collaborating neurologists in Sydney, at the University of Sydney, the offices of MS Australia, and Neuroscience Research Australia. As described above contact details of a research staff member will be made available in the flyers and invitation letters. People with MS who are interested in the study will initiate the contact with our research member.

* 1. **Eligibility Criteria**

Participants with MS who can walk independently (with or without the use of an assistive device) will be invited to participate. Participants will be screened and excluded from the study if they have had a relapse within the last 3 months, corticosteroid treatment within 28 days of the study commencement, or have contra­indications for exercise.

* + 1. **Inclusion Criteria**

See 5.2

* + 1. **Exclusion Criteria**

See 5.2

## Informed Consent Process

Written informed consent will be obtained prior to entry into either project. The participant will receive an explanation of the project and directed to read the Information Sheet. Both the Information sheet and Consent form comply with requirements of the University of Sydney.

* 1. **Enrolment and Randomisation Procedures**

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study enrolment code and this will be documented on all study documents.

* 1. **Blinding Arrangements**

Outcome measures will be assessed at the end of the intervention (week 10) by a trained blinded assessor.

* 1. **Breaking of the Study Blind**
     1. **On Study**

Blinding will be broken after collection of all data from the first intervention block (assessments at the end of the 10wk intervention and collection of falls dairies of the subsequent 10wks for the same participants). Only the honours student will be unblinded to the assessment data to perform an interim analysis of the data for a preliminary report as part of a thesis. All other assessors will remain blinded to allocation.

* + 1. **Following Completion of the Study**

At the conclusion of the study all data will be unblended and analysed.

* 1. **Participant Withdrawal**
     1. **Reasons for withdrawal**

Participants can withdraw from the study at any time by signing the Revocation of Consent form at the end of the Information and Consent form. Participants can also choose to withdraw their data by ticking the box on the Revocation of Consent form.

* + 1. **Handling of withdrawals and losses to follow-up**

The possible circumstance that the study might be terminated early is that number of participants who withdraw is large enough to significantly impact on the statistic power. If this (unlikely) circumstance does occur, the research team will discuss and take appropriate actions such as informing participants, correspondence to HREC, compiling a final study report, unbinding if applicable

* 1. **Trial Closure**

Once the study is complete there will be no further follow up.

* 1. **Continuation of therapy**

**NA**

# STUDY VISITS AND PROCEDURES SCHEDULE

## Study Flow Chart for Project 1

Enrolment/

Assessment

Randomisation

Treatment Phase

(10 weeks)

WBV group Exercise group

Overall timeline for all hypotheses is as follows:

Project organisation.

Assessment will occur at the start of that participant’s intervention block and at the end of 10 weeks. Assessment will include administering the PPA, Timed Up and Go, the CSRT, 6 Minute Walk, and the MSFC score. For 50 participants, a second assessment will occur 1 week after the initial assessment (not shown on chart)

Training consists of a home visit session for each participant to be trained in the selected exercises and for familiarisation and use of the WBV platform, including a mid-intervention home visit. .

# CLINICAL AND LABORATORY ASSESSMENTS

NA

# ADVERSE EVENT REPORTING

Adverse events (such as injuries associated with prescribed exercises) and falls will be monitored and recorded throughout the study for both groups via monthly telephone calls. Falls will be reported as the primary outcome of the study. The number and type of injuries will also be reported. Participants will be asked to report any adverse event that occurs while performing the prescribed exercises as soon as possible to the investigators. Any serious or unexpected adverse events will be reported within 72 hours of notification to the HREC.

# STATISTICAL METHODS

* 1. **Sample Size Estimation**

The sample size was selected based on several factors. First, the project’s primary aim is to assess prospective falls as a pilot project. However, the sample size needed to properly power a study to only examine prospective falls would likely be >200 (5). However, falls risk as assessed by the PPA is a good predictor of prospective falls (9) and has been validated in people with MS (5). Using data from a previous study (5) showing that falls risk score using the PPA is 2.7 (± 1.38) for people with MS (Disease Steps 0-5), we conducted a power and sample size analysis in STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). The result showed a sample size of 108 (N1 = 54; N2 = 54; ratio: 1:1) will give 90% power to detect ~30% difference for falls risk using the PPA, assuming the use of a two‑tailed independent samples t-test with alpha = 0.05 (In Stata: power twomeans 0, diff(.87) sd(1.38) power(0.9)). Next, based on the recent findings of Uszynski and colleagues (11) a sample size of 104 is recommended to show differences in our secondary outcome examining functional mobility using the 6 Minute Walk test. To confirm this, we again conducted a power and sample size analysis in STATA using data from a previous study showing that people with MS in Disease Step 3 (or EDSS = ~4.5‑5.5) walk ~315 meters (SD = 85) in 6 minutes (6). The result showed a sample size of 88 (N1 = 44; N2 = 44; ratio: 1:1) will give 90% power to detect ~20% difference for the 6‑minute walk test outcome variable, assuming the use of a two-tailed independent samples t-test with alpha = 0.05 (In Stata: power twomeans 0, diff(60) sd(85) power(0.9)).

With respect to reliability of outcome tests, a sample size of 50 participants provides an adequate sample size and narrow confidence intervals to sufficiently analyse reliability of the choice stepping reaction time test, the physiological profile assessment, and the multiple sclerosis functional composite score for people with MS.

* 1. **Population to be analysed**

People with MS who meet the criteria to participate in this study

* 1. **Statistical Analysis Plan**

Between group comparisons of final test performance for the outcome measures will be made using General Linear Models (ANCOVA) controlled for pre-test performance. Significance is set at 0.05. Change scores (pre minus post) and effect sizes will be calculated. An estimate of the effect on falls will also be calculated to inform sample size calculations for any future trial to determine the effect on the intervention on fall rates. Participants can withdraw from the study at anytime. However, this is an intention to treat study and thus, all data collected will be included in the final analysis except if participants opt to withdraw their data.

* 1. **Interim Analyses**

**NA**

# DATA MANAGEMENT

* 1. **Data Collection**

All assessment data will be taken at The University of Sydney and NeuRA and recorded in lab manuals or hard drives. All digital data collected at NeuRA will be stored on the University of Sydney’s network server via VPN.

* 1. **Data Storage**

Data will be stored on the University of Sydney’s network server, accessible by password to the investigators. Laboratory notebooks will remain in secured laboratories/offices Neurological Rehabilitation Research Offices, Rm S246 and/or Rm S247, Bld C43.

* 1. **Data Confidentiality**

During data analysis participants’ identifiers will be removed and replaced by a randomly designated participant ID (numeric code) to be used in laboratory notebooks and data collection sheets. All study materials will be accessible only by password on the University’s server. All hard copy materials will be secured in laboratories/offices Neurological Rehabilitation Research Offices, Rm S246 and/or Rm S247, Bld C43. Information will be stored in potentially re­identifiable form should the need arise in the future. The code will be stored in a locked filing cabinet in the Neurological Rehabilitation Research Offices, Rm S246 and/or Rm S247, Bld C43 , with access for the code restricted to the Chief Investigator only.

**Study Record Retention**

20 years per University of Sydney requirements.

# ADMINISTRATIVE ASPECTS

* 1. **Independent HREC approval**

**Not applicable**

* 1. **Amendments to the protocol**

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

* 1. **Protocol deviations**

Any protocol deviations will be submitted to the HREC for review.Participant reimbursement

* 1. **Financial disclosure and conflicts of interest**

There are no conflicts of interests.

# USE OF DATA AND PUBLICATIONS POLICY

Results will be reported at scientific conferences and published in journals, and student theses.

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