BMJ Open

# Balance on the Brain: A randomised controlled trial evaluating the effect of a multimodal exercise program on physical performance, falls, quality of life and cognition for people with mild cognitive impairment: Study protocol

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2021-054725 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 23-Jun-2021 |
| Complete List of Authors: | Burton, Elissa; Curtin University - Perth City Campus, Curtin School of Allied Health<br>Hill, Keith; Monash University, School of Primary and Allied Health Care<br>Ellis, Kathryn; University of Melbourne, The Academic Unit for Psychiatry of Old Age, Department of Psychiatry; University of Melbourne, Melbourne School of Psychological Sciences<br>Hill, Anne-Marie; Curtin University, School of Physiotherapy and Exercise Science<br>Lowry, Meggen; Next Step Health<br>Moorin, Rachael; Curtin University, Curtin School of Population Health; University of Western Australia, School of Population and Global Health<br>McVeigh, Joanne; Curtin University, Curtin School of Allied Health; University of Witwatersrand, School of Physiology<br>Jacques, Angela; Curtin University, Curtin School of Allied Health<br>Erickson, Kirk; University of Pittsburgh, Center for the Neural Basis of Cognition; Murdoch University, College of Science, Health, Engineering, and Education<br>Tate, Joel; Armadale Health Service, Department of Rehabilitation and Aged Care<br>Bernard, Sarah; Sir Charles Gairdner Hospital Group, Department of Rehabilitation and Aged Care<br>Orr, Carolyn; Royal Perth Hospital, Cognitive Clinic<br>Bongiascia, Luke; Rockingham Peel Group, Physiotherapy Department, Adult Community and Allied Health Directorate<br>Clarnette, Roger; University of Western Australia, Medical School<br>Clarke, Melanie; North Metropolitan Health Service Mental Health, Public Health and Dental Services, Neurosciences Unit<br>Williams, Shannon; Royal Perth Hospital, Neurogenetic Clinic and Physiotherapy Department<br>Lautenschlager, Nicola; University of Melbourne, Academic Unit of Psychiatry of Old Age; The Royal Melbourne Hospital, NorthWestern Mental Health |
| Keywords: | PUBLIC HEALTH, REHABILITATION MEDICINE, PREVENTIVE MEDICINE |
| | |

# Balance on the Brain: A randomised controlled trial evaluating the effect of a multimodal exercise program on physical performance, falls, quality of life and cognition for people with mild cognitive impairment: Study protocol.

**Short title:** Balance on the Brain Study Protocol

Elissa Burton[1], Keith D Hill[2], Kathryn A Ellis[3,4], Anne-Marie Hill[1], Meggen Lowry[5], Rachael Moorin[6,7], Joanne McVeigh[1,8], Angela Jacques[1], Kirk I. Erickson[9,10], Joel Tate[11], Sarah Bernard[12], Carolyn F Orr[13], Luke Bongiascia[14], Roger Clarnette[15], Melanie L Clark[16], Shannon Williams[17], Nicola T Lautenschlager[3,18].

[1]Curtin School of Allied Health, Faculty of Health Sciences, Curtin University, Perth, Australia

[2]Rehabilitation, Ageing and Independent Living (RAIL) Research Centre, School of Primary and Allied Health Care, Monash University, Melbourne, Australia

[3]Academic Unit for Psychiatry of Old Age, Department of Psychiatry, The University of Melbourne, Melbourne, Australia

[4]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia

[5]Next Step Health, Brisbane, Queensland

[6]Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Perth, Australia

[7]School of Population and Global Health, The University of Western Australia, Perth, Australia

[8]Movement Physiology Laboratory, School of Physiology, University of Witwatersrand, South Africa

[9]Department of Psychology, Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, United States of America

[10]Murdoch University, College of Science, Health, Engineering, and Education, Perth, Western Australia

[11]Department of Rehabilitation and Aged Care, Armadale Health Service, Perth, Australia

[12]Department of Rehabilitation and Aged Care, Sir Charles Gairdner Hospital Group, Perth, Australia

[13]Cognitive Clinic, Royal Perth Hospital, Perth, Australia

[14]Physiotherapy Department, Adult Community and Allied Health Directorate, Rockingham Peel Group, Rockingham, Australia

[15]Medical School, University of Western Australia, Crawley, Australia

[16]Neurosciences Unit, North Metropolitan Health Service Mental Health, Public Health and Dental Services, Perth, Australia

[17]Neurogenetic Clinic and Physiotherapy Department, Royal Perth Hospital, Perth, Australia

[18]NorthWestern Mental Health, Royal Melbourne Hospital, Australia

Corresponding Author:
Dr Elissa Burton
Senior Research Fellow
Curtin School of Allied Health
Faculty of Health Sciences
Curtin University
Perth, WA, Australia
PO Box U1987
Perth WA 6845
Email: E.Burton@curtin.edu.au

**Word Count**: 4857

**Keywords**: mild cognitive impairment, balance, exergame, falls, quality of life, cognition.

# Balance on the Brain: A randomised controlled trial evaluating the effect of a multimodal exercise program on physical performance, falls, quality of life and cognition for people with mild cognitive impairment: Study protocol.

**Short title:** Balance on the Brain Study Protocol

**Abstract:**

**Introduction**: Exercise and physical activity have been shown to improve cognition for people living with mild cognitive impairment (MCI). There is strong evidence for the benefits of aerobic exercise and medium evidence for participating in regular strength training for people with MCI. However, people living with MCI fall twice as often as those without cognitive impairment and the evidence is currently unknown as to whether balance training for people with MCI is beneficial, as has been demonstrated for older people without cognitive impairment. The aim of this study is to determine whether a balance-focused multimodal exercise intervention improves balance and reduces falls for people with MCI, compared to a control group receiving usual care.

**Methods and Analysis**: This single blind randomised controlled trial (Balance on the Brain) will be offered to 396 people with MCI living in the community. The multi-modal exercise intervention consists of two balance programs and a walking program to be delivered by physiotherapists over a 6-month intervention period. All participant will be followed up over 12 months (for the intervention group this involves 6 month intervention and 6 months maintenance). The primary outcomes are 1) balance performance and 2) rate of falls. Physical performance, levels of physical activity and sedentary behaviour, quality of life and cognition are secondary outcomes. A health economic analysis will be undertaken to evaluate the cost effectiveness of the intervention compared with usual care.

**Ethics and Dissemination**: Ethics approval has been received from the South Metropolitan Health Service (SMHS) Human Research Ethics Committee (HREC), Curtin University HREC, and the Western Australia Department of Health HREC; and approval has been received to obtain data for health costings from Services Australia. The results will be disseminated through peer-review publications, conference presentations, and on-line platforms.

**Registration Details**: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620001037998.

**Keywords**: mild cognitive impairment, balance, exergame, falls, quality of life, cognition.

## Strengths and Limitations of this Study

- To our knowledge this is the first randomised controlled trial for people living with MCI that will evaluate the effect of exercise on improving balance and reducing falls.
- An economic evaluation from a healthcare perspective allows for potential future implementation should the intervention be effective.
- Participants will be monitored regularly with monthly follow-up phone calls collecting physical activity, health and falls data.
- The study is statistically powered for both primary outcomes (i.e. balance and falls), baseline and outcome assessors are blinded to group allocation.
- A limitation may be convenience sampling (i.e. one state) rather than population-based sampling (i.e. multi-state) which may not be representative of the Australian MCI population.

## INTRODUCTION

The prevalence of mild cognitive impairment (MCI) varies between 20% for those aged 70+ years in USA,[1] 18.5% in China for those aged 60 and over,[2] up to 37% for Australians aged 70-90 years [3] and leads to an increased risk of dementia.[4] According to the International Working Group on MCI the core features of MCI include: evidence of deterioration in cognition either objectively measured over time and/or through self-report or by an informant reporting cognitive deficits beyond that expected for age and education level; the person not presenting with dementia; and activities of daily living being preserved, although there may be some mild impairment in complex activities.[5, 6]

People with MCI are more likely to fall than those of the same age without cognitive impairment.[7] The average age of the population is increasing, therefore MCI and falls are likely to affect thousands more Australians as they age. This will not only negatively affect individuals and their families but will have a significant impact on health budgets over the coming decades unless successful interventions are developed and implemented widely (i.e. Australian falls-related costs estimated at $648 million in 2007-2008,[8] and falls are the leading cause of injury-related hospitalisations in Australia,[9] with age standardised rates increasing at >2% per annum).[10]

For older people living in the community without cognitive impairment, balance exercise programs that mainly contain balance and functional training components have been shown to be one of the most effective measures for decreasing the risk and rate of falling.[11] Unfortunately, the evidence for people living with MCI and/or other cognitive impairments is less clear. Five randomised controlled trials [12-16] have been conducted with people with MCI which have included measuring falls or fear of falling, however none have specifically used a balance exercise program, nor followed participants for a long period of time (6-12 months) with falls being the primary outcome.

Recently developed physical activity guidelines for older Australians with MCI or subjective cognitive decline (SCD), recommended the same amount of aerobic, strength and balance exercise per week as the guidelines for all older adults (i.e. 150 minutes moderate intensity aerobic activity, plus two strength and balance sessions per week [17]), largely because there is a lack of evidence to make specific recommendations for this population.[5, 18] The guidelines noted there were no research trials specifically examining balance interventions in older adults with MCI and subjective cognitive decline and therefore their current recommendations were extrapolated from studies of older adults with no cognitive impairment.[18] A systematic review by Burton et al.[19] also showed few balance interventions have been undertaken to reduce falls for people living with dementia. Maintaining

balance as one ages is critical for participating in everyday activities, staying mobile, living independently and reducing the risk of falling.[20]

Despite a number of additional randomised controlled trials evaluating exercise interventions in people with MCI since the publication of these recommendations, there remains a gap in the research and a critical need to better understand whether balance can be improved for people with MCI living in the community and if so, whether improved balance is translated into fewer falls. This project provides an opportunity to address these important research gaps and assist people with MCI, their caregivers, healthcare providers and potentially reduce the cost of healthcare into the future.

The aims of this research are to determine whether a balance-focused multimodal exercise intervention improves balance and reduces the rate of falls for people with MCI, compared to a control group (receiving usual care and a health promotion flyer). The study also aims to evaluate the cost effectiveness of the intervention compared with usual care. Secondary aims include evaluating the effect of the intervention on physical performance and quality of life and reducing cognitive decline.

It is hypothesised that older adults with MCI participating in the balance-focused multimodal exercise intervention, when compared to the usual care group (control), will (during the intervention and for the following 6 months) achieve:

a. improved balance (improvement on 4-square step test [21]);
b. a decrease in falls rate (using monthly calendar and phone calls);
c. improved physical performance (improvement in the Short Physical Performance Battery (SPPB),[22] Timed-Up-And-Go (TUG),[23] 6 minute walk test (6MWT) [24]) and physical activity (increase in step count using activPAL4 accelerometers);
d. improved quality of life (improvement on Quality of Life – Alzheimer's Disease (QOL-AD) [25, 26];
e. a reduction in rate of cognitive decline (Montreal Cognitive Assessment (MoCA)[27]).

It is also hypothesised that the exercise program will be cost-effective compared with usual care, defined as having an incremental cost-effectiveness ratio of less than $50,000/QALY gained. In addition, the cost per fall per will be evaluated.

## METHODS AND ANALYSIS

### Study Design

This will be a single blind randomised controlled trial (RCT), comparing a balance-focused multimodal exercise intervention to a usual care control group for people with MCI (see Figure 1). The CONSORT statement [28] has been used as a framework for developing the project methodology.

**Participants**

Three hundred and ninety-six participants living with MCI will be recruited across the Perth and Rockingham metropolitan areas of Western Australia. Participants will be included if they meet the following criteria: aged over 50 years; living in the community with a diagnosis of MCI consistent with the Petersen criteria,[29] including self-reported memory complaint, a Clinical Dementia Rating [30] (CDR) of 0.5; and Standardised Mini-Mental Status Examination [31] (SMMSE) score of 24 or above. Other inclusion criteria are: not meeting Australian physical activity guidelines (i.e.<150 minutes of moderate intensity physical activity a week self-reported) and not participating in balance training regularly (i.e.< twice a week).

Participants will be excluded if they have an unstable medical condition, terminal illness, diagnosis of significant cognitive impairment and/or chronic mental illness (e.g. schizophrenia), severe sensory impairment affecting mobility, live in residential aged care, drink more than 4 standard alcoholic drinks per day (i.e. >28/week), score >6 for the Geriatric Depression Scale-15 item (GDS-15) [32] or have a lack of fluency in written and spoken English.

**Recruitment and Screening**

Participants will be recruited from the community via 9 memory cafes that are held throughout Perth and organised by Alzheimer's Western Australia (WA), advertisements in the local media including CurtinFM radio, The Senior and Have a Go newspapers, and where possible through news segments on television. Alzheimer's WA will also forward enquiries from people with MCI who wish to participate. A Facebook page providing up to date information about the project will be developed and advertisements sent out promoting the study. Memory clinics at Armadale Hospital, Fremantle Hospital, and Sir Charles Gairdner Hospital, the Royal Perth Cognitive Disorder Clinic, the Aged Care Rehabilitation clinics, at Rockingham General Hospital, the Aged Care Assessment Team (ACAT), the Regional Assessment Service (RAS) and the Neurosciences Unit will all assist with recruitment.

The research team will contact potential participants by telephone to check the suitability of the person in accordance with the inclusion and exclusion criteria using a screening protocol. The telephone screen includes a description of the study, questions about memory, current

physical activity levels, living situation, availability over the following 6 month period, cognitive screen (i.e. TICS-M), health screening (i.e., vision, hearing, medical conditions), alcohol consumption, and the GDS-15. The GDS-15 is included in the screening to determine the presence of clinically relevant symptoms of depression. If the participant reports a medical diagnosis of depression they will not be required to complete the GDS-15. The full phone screening tool is available from the corresponding author and takes approximately 45 minutes to complete. The contact details of the participant and their general practitioner will also be collected.

To complete the screening process the Research Officer will meet with the potential participant face-to-face at a location comfortable for both parties and complete the questions required to determine a diagnosis of MCI for this study (see inclusion criteria). This includes a self-reported memory complaint, completing the CDR and receiving a score of 0.5 and the SMMSE with a score of ≥24, or diagnosis from medical specialist (e.g. Geriatrician, Neurologist). If these criteria are met, participants will be asked if they have read the Participant Information Sheet and Consent Form (if not they will be asked to read it then) and have any questions about participation in the trial answered. Prior to commencing in the study each participant will provide written consent.

**Outcomes and Assessments**

An overview of the primary and secondary outcomes and assessment tools to measure each outcome are presented in Table 1. All assessments are valid, reliable and have been trialled with people with MCI. Participants will be closely supervised during all balance and mobility assessment tasks, as is routine practice when using these assessment items. To ensure standardisation of procedures, the Research Officers collecting the data will be trained by the same Chief Investigator who has a background in exercise science.

All participants will be assessed at baseline, six months (i.e., completion of the intervention period) and 12 months. This study will have two primary outcomes:

1) balance: measured using the four square step test
2) falls rate: measured using monthly calendars and follow-up phone call. A fall will be defined as “an unexpected event in which the individual comes to rest on the ground, floor or lower level” [33] as recommended by the Prevention of Falls Network Europe.

**Table 1 Assessments and timelines for Balance on the Brain**

| Measure | Outcome (Primary / Secondary) | Phone / Home Screen | Baseline | 6 Months | 12 Months |
|---|---|---|---|---|---|
| Geriatric Depression Scale – 15 Item | | X | | | |
| Modified Telephone Interview for Cognitive Status (TICS-M) | | X | | | |
| Standardised Mini-Mental State Examination (SMMSE) | | X | | | |
| Cognitive Dementia rating (CDR) | | X | | | |
| Balance: Four Square Step Test (4SST) [21, 34] | Primary | | X | X | X |
| Primary falls: collected using a monthly call and calendar | Primary | | Monthly phone call and calendar | | |
| Physical performance: Short Physical Performance Battery (SPPB) Test [22, 35, 36] | Secondary | | X | X | X |
| Physical performance: Timed Up and Go (TUG) Test [23] | Secondary | | X | X | X |
| Physical performance: 6 Minute Walk Test (6MWT) [24] | Secondary | | X | X | X |
| Physical activity: Accelerometer worn for 7 days (ActivPAL4) (step count and time spent in moderate to vigorous physical activity) | Secondary | | X | X | X |
| Physical activity: Physical Activity Scale for the Elderly (PASE) administered a week after each assessment (at accelerometer pick up) [37-39] | Secondary | | X + 1 week | X + 1 week | X + 1 week |
| Quality of Life: Quality of Life – Alzheimer's Disease (QOL-AD) [25, 26] | Secondary | | X | X | X |
| Cognition: Montreal Cognitive Assessment (MOCA) Test [27] | Secondary | | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| Secondary falls: number of fallers, injurious falls | Secondary | | Monthly phone call and calendar | | |
| Falls efficacy: Falls Efficacy Scale – International (FES-I) [27] | Secondary | | X | X | X |

*Note.* An injurious fall will be defined as a fall where the participant sought "medical advice." Data will also be collected on any injury sustained such as bruising, laceration, fracture, loss of consciousness or if the participant reports ongoing pain.[40, 41]

The four square step test (dynamic standing balance) uses four walking sticks/poles/pvc pipes to create four squares (i.e. quadrants).[21] To complete the test the participant steps both feet into each quadrant in a clockwise direction, then in an anti-clockwise direction back to the starting position, without touching the poles.[21] Two full trials are completed and the fastest time is reported.

All study participants will be asked to complete a monthly calendar that includes falls information (i.e., fall and date occurred), changes to health and self-reported physical activity. This will be followed up each month with a phone call to collect these data (i.e., falls, changes to health, physical activity). Falls data collected during the phone call will include number of falls, where they occurred, injuries, medical attention required etc.

The SPPB groups a number of physical performance measures such as gait speed, chair stand and balance tests into one test.[42] It has been used to monitor function in older people and those with MCI as well as predict possible disability, risk for mortality and residential aged care admission. Scores range from 0 (worst performance) to 12 (best performance).

The TUG test is used to measure a person's mobility but also includes the ability to stand up from a chair, walk three metres, turn, walk back and sit down in the chair.[23] The participant will be timed using a stop watch. Each participant will be given a practice trial that is not timed and then asked to complete the TUG.

The 6 minute walk test (6MWT) is a sub-maximal exercise test used to assess walking endurance and aerobic capacity.[24] Participants will walk around a circuit which is at least 12 metres long for 6-minutes with the distance calculated at the end of this time. The circuit will be marked by using bright coloured cones.

Physical activity will be measured using ActivPAL4™ accelerometers. The activPAL™ is currently considered the most accurate field-based measure of sitting time and sit-to-stand transitions.[43] The accelerometers will be worn, and data collected over a 7 day period at baseline, 6 and 12 month data collection. ActivPAL™ data will be converted to event level files

using propriety PAL Technologies software. The following variables will be derived from the accelerometer data across the 7 days: step count, time spent in sedentary, upright and stepping activities, stepping intensity (cadence), and duration of lying, sitting, standing and stepping activities. The activPAL4™ will be worn on the thigh, is waterproof and does not need to be removed for the 7 days. The accelerometer will be applied by research staff using a Tegaderm dressing and removed by the research staff on return. Each device is small (23.5mm x 43mm x 5mm) and weighs 9 grams.

The Physical Activity Scale for the Elderly (PASE) is a 12-item self-report instrument designed to assess physical activity levels in older people over a 1-week period.[37] It combines physical activity information during leisure, household, and occupational activity.[44] A score is calculated based on activity frequency and an activity-weighted score multiplied by frequency.[39] The higher the PASE score, the more physically active a person is, with PASE scores ranging from zero to 400.

The Quality of Life in Alzheimer's Disease (QOL-AD) tool is a 13-item measure designed to obtain a rating of quality of life.[25, 26] Each question is rated on a four point scale, 1 being poor and 4 being excellent, total scores range between 13-52.[25, 26] It was specifically designed for people with cognitive impairment.

Cognition will be assessed using the Montreal Cognitive Assessment (MoCA), which assesses eight cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation.[27] The total maximum score is 30 points and the research staff will administer it face to face.[27]

The Falls Efficacy Scale – International (FES-I) is a 16-item tool used to measure "concerns about falling" and is recommended to be administered face-to-face for people with cognitive impairment.[45] Participants will be asked to answer each question on a Likert scale from "not at all concerned" (1) through to "very concerned" (4), based on whether they think they would be concerned about falling while participating in the activities, e.g. *How concerned are you about falling while cleaning the house (e.g. sweeping, vacuuming, or dusting)?*

**Randomisation and Blinding**

A concealed, computer-generated sequence of randomly selected permuted blocks (block size = 6) in a 1:1 ratio will be generated by a statistician not involved in the study. A staff member (external to the study) from Curtin University's Clinical Trials Data Management Centre will enter the randomisation codes into the REDCap project data management system, minimising bias by concealing randomisation. Once a participant has been recruited and they provide written consent to participate, baseline data collection will be undertaken by Research

Officer staff. After baseline data collection is completed and has been entered into REDCap by a Research Officer the lead researcher will then press the randomisation button. An email will be automatically sent by the REDCap project system to the lead researcher (independent, not involved in assessments or intervention) who will allocate each intervention participant to a physiotherapist delivering the intervention. This email will include the contact details (i.e., name, phone number and address) of the participant allocated to the intervention group, to allow the physiotherapist to contact them directly.

The Research Officers who enrol the participants, collect and enter baseline, 6 and 12 month data will be blinded to group allocation throughout the study (Figure 1). Those delivering the intervention (i.e., physiotherapists) will not be involved in any study outcome data collection after randomisation has occurred (except for the process evaluation of the intervention delivery – separate study, methods not reported in this paper). Participants cannot be fully blinded to receiving the intervention. Participants will be reminded at each outcome assessment (i.e., baseline, 6 months and 12 months) not to divulge their group assignment to research staff or other participants (i.e., who may attend the same memory café).

*Insert Here* **[Figure 1. Study Design]**

**Intervention**

The intervention period will be 24 weeks and the data collection/follow-up periods 6 and 12 months post baseline. The balance-focused multimodal exercise intervention group will participate in the Balance Yourself (a book) [46] and Clock Yourself Programs (exergame App or CD) [46] and in discussion with the physiotherapist progress (where appropriate) to walking 30 minutes per day, five days a week in a safe environment. Both balance programs are safe and have been delivered by experienced physiotherapists for over five years to approximately 500 older adults, including some individuals with stroke, Parkinson's Disease, MCI or early-stage dementia. These complementary programs aim to build a person's capacity to prevent falls. The Balance Yourself program aims to improve balance, whereas the Clock Yourself program aims to improve stepping reactions in all directions in the event that a person should lose their balance. Each program starts slowly and progresses over time through levels of increasing difficulty in accordance with each participants' ability. The Balance Yourself book, which has been adjusted specifically for people with MCI, guides the user to practise evidence-based balance exercises which are introduced in a progressively challenging sequence. The standing balance exercises involve standing still, and are progressed in difficulty with

narrowing foot positions and then introducing head movements, reaching outside the base of support, closing eyes and dual tasking. The dynamic balance exercises involve stepping or walking in various directions and with narrowing foot positions e.g. sideways, backwards, tandem, figure of 8.

The Clock Yourself program is presented as a brain game to help people think faster on their feet. It is a volitional stepping method designed to progressively improve physical agility and stepping reaction times while a person's attention is divided. The program is deliverable by either an app (low-tech) or a set of audio CDs (no-tech). To cater for heterogeneity in tech-literacy and to promote self-efficacy with the exercise, participants can choose whichever tool they are most confident with. A guidebook is also available to assist participants to navigate the app or the CDs. Participants will be asked to progress throughout the 24-week intervention to participating in 60 minutes of the Balance Yourself program and Clock Yourself program per week, for a total of 120 minutes of balance exercise per week (i.e., 20 minutes per day). Where required, carers will be asked to support the participants to carry out the exercise programs e.g., guiding them with safe set up or providing reminders.

The walking component will be individually tailored to each participants' abilities, with emphasis on walking environments to maximise safety. Participants will be encouraged to progress to walking 30 minutes a day, 5 times a week over the 24-week intervention.

The physiotherapists will deliver the intervention approximately 7-10 days after group allocation (i.e., to intervention group), they will return for further home visits in weeks 2, 8, 12, 17 and 20 of the intervention to provide advice on technique, use of the intervention tools and progressing through the levels of exercise. Motivational phone calls will be made by the physiotherapist in weeks 3, 6, 10, and 14 of the intervention. (See Figure 2). Each intervention participant will be asked to practice the balance and walking programs progressing over time to 5-7 days a week (or up to 120 minutes for the week for the balance programs, plus a minimum of 30 minutes per day walking).

*Insert Here* **[Figure 2. Timeline of intervention delivery by physiotherapists]**

**Control Group**

The usual care group will receive a health promotion education leaflet, after completing baseline data collection. This will include documentation on the current physical activity

recommendations for people with MCI and healthy eating and drinking recommendations. The intervention group will also receive the same education leaflet.

**Sample Size**

The sample size was calculated separately for the two primary outcomes: 1) balance, based on the four square step test) and 2) falls rate. The sample size for the balance outcome was calculated based on detecting a minimum effect size difference of 0.18 [47] over 3 time points between intervention and control groups, with 80% power and alpha=0.05. After assuming a 20% withdrawal rate over the 24 week intervention, and a further 15% loss to follow up over the following 6-month follow-up, consistent with other similar studies[48] a total of 212 participants (106 per group) is required.

The sample size for falls rate outcome was based on detecting a 30% minimum relative reduction in the falls rate (0.5 to 0.35) in the intervention group compared to the control group, with 80% power and alpha=0.05. After assuming a 20% withdrawal rate over the 24 week intervention, and a further 15% loss to follow up over the following 6-month follow-up, a sample size of n=396 is required (198 per group). Therefore a sample size of 396 participants will be required for the overall study (G*Power 3.1.9.2).

**Statistical Analysis**

Continuous data will be summarised as means and standard deviations or medians and interquartile ranges and compared using t-tests or Mann-Whitney U tests, depending on normality. Categorical data will be summarised using frequency distributions and compared using $\chi^2$ tests. The primary outcomes will be analysed at baseline, 6 and 12 months using generalised linear mixed-effects models which use Maximum Likelihood Estimation methods (MLE) to account for data missing at random. Imputation methods will not be used as they lead to potential bias. The primary outcome of falls rate will be analysed using negative binomial regression, with adjustment for participant's observation time in the study. Models will be summarised using predicted mean estimates, weighted mean differences and 95% confidence intervals. All final measures, regardless of intervention participation or compliance will be collected. Analysis will be performed on both intention-to-treat and per-protocol basis. Stata version 16.0 will be used for data analysis, with significance level set at 0.05.

**Economic Analysis**

Two forms of economic analyses will be undertaken: 1) a cost-utility analysis using the QOL-AD to assess the incremental cost of Quality adjusted life years (QALYs) gained; and 2) a cost-effectiveness analysis to assess the incremental cost per fall prevented. Both analyses will be undertaken from a healthcare system perspective

Given an RCT is being undertaken to determine the effectiveness of intervention, the economic evaluation will reflect a service substitution model without cost sharing or transfer. Costs of the program will be evaluated using prospective data collection for each participant and will include the costs associated with the intervention and outcomes using a healthcare system perspective. Program costs in addition to those for usual care will include:

- Training the physiotherapists to deliver the two balance programs (i.e. Balance Yourself and Clock Yourself) and the progressive walking program
- Physiotherapists salary to deliver the intervention
- Costs associated with outcomes for (all) participants (regardless of group) include:
    - Cost of Emergency Department (ED) visits
    - Cost of in-patient hospitalisation
    - Cost of ambulance use
    - Cost of General Practitioner (GP) and other Medicare subsidised out-of-hospital services (Medicare Benefits Scheme: MBS)
    - Cost of Pharmaceutical Benefits Scheme (PBS) medication.

Inpatient costs will be calculated using Diagnostic Related Group (DRG) based costings using the appropriate Independent Hospital Pricing Authority (IHPA) National Efficient Price Determination report. Cost of ED attendances will be based on urgency related/disposition group (derived using Episode End Status, Type of Visit, Triage, Sex, and Diagnosis Code) and costed using Independent Hospital Pricing Authority (IHPA) National Efficient Price Determination report or cost report.

Ambulance utilisation will be costed at $986 per service. The cost of MBS services will be ascertained directly from the data (schedule fee, actual fee paid). PBS supported medication costs will be ascertained using the relevant PBS prescription charges (i.e. for general and health care card beneficiaries).

Effectiveness of the intervention will be measured using the framework of a within trial cost utility analysis using the QOL-AD mapped across to the EQ-5D-5L utility algorithm weighted for the Australian population to derive an overall index of the health state utility at each time point. Participant (i.e. intervention and controls) health state utilities will be captured at baseline, 6 and 12 months post recruitment.

An incremental cost-utility analysis will be undertaken to compare the mean incremental cost and QALY profiles for each group according to intervention status. The QALY profile for each intervention participant will be calculated using area under the curve methods. Where a significant difference occurs between the groups an incremental cost-effectiveness ratio

(ICER) for QALYs gained based on utilities derived from the mapped EQ-5D-5L will be calculated.[49] Using the average costs for the intervention and the mean QALYs gained for the intervention, the incremental cost of the intervention will be compared to the control group and calculated and then plotted on a cost-effectiveness plane.[50] To estimate a distribution around costs and QALYs gained, and to calculate the confidence intervals around the ICERs to account for joint uncertainty in costs and QALYs gained, bootstrapping will be applied.[50] After conducting one-way and probabilistic sensitivity analysis incorporating all key variables, a cost-effectiveness acceptability curve will be plotted.[50] This will provide information as to whether the intervention is cost-effective, based on a decision maker's willingness to pay for each additional QALY gained (i.e. <$50,000/QALY gained).[50]

Cost effectiveness will also be estimated by utilising measurement of the change in other outcomes (e.g. falls rate, falls injuries) where a significant difference is observed between the intervention and control groups. Confidence intervals will be presented around the incremental cost effectiveness ratios (ICER) and cost effectiveness acceptability curves for varying threshold values of cost effectiveness will be presented. A 12-month time horizon will be used and a healthcare system perspective using within trial probabilities and costs will be undertaken. Assessment of the sensitivity of the results obtained to variation in measured effectiveness, healthcare resource use, intervention and usual care unit costs and participant groups will be undertaken using one-way and probabilistic sensitivity analysis, as per best practice guidelines.[51]

**Data management**

All data will be collected and stored in Curtin University's REDCap data management system (redcap.curtin.edu.au) which uses a secure-socket-layer to encrypt the web transport layer with 2 step authentication (i.e., email or mobile). Anyone accessing this project database must provide a valid username, password and code at each log in. Each data entry instance into the REDCap file is logged. All other electronic data and information connected to this study will be kept in a password-protected Curtin University R-Drive folder only accessible by the Chief Investigators and research staff.

**Data Monitoring**

The project will be managed by a steering committee that includes the Chief investigators and representatives of the Associate Investigators/Advisory Group. The steering committee will monitor (including audits) the conduct and progress of the research project and ensure that project milestones are being met; study procedures are being adhered to; and provide guidance about the project implementation. The committee will meet and report half-yearly

throughout the project. The committee will report to the appointed hospital representatives and the Ethics Committee Chairs where required. A Data Monitoring Committee (DMC) external to the study investigators will be formed and the committee will receive updates every six-months (or earlier if applicable). The aim of the DMC is to safeguard the interests of the study participants and assess the safety and integrity of the intervention. The DMC will include a person with previous experience serving on a DMC and an experienced physiotherapist and/or researcher.

**Harms**

Adverse events will be documented across the 6 month intervention either by physiotherapists during intervention visits/phone calls or by research staff during monthly follow up calls to participants to collect data about adverse events, possible falls and health issues from the preceding month documented in monthly calendars. Any significant adverse events will be reported to the Human Research Ethics Committee.

**Patient and Public Involvement Statement**

Two consumer representatives living with memory issues have been involved with the project since it was funded. They have assisted with the language in the Participant Information and Consent Forms and all documentation that will be read or received by the Balance on the Brain participants. They have also provided feedback on completing the monthly calendar and will continue to provide their expertise and feedback across the duration of the project.

**ETHICS AND DISSEMINATION**

Ethics approval for this study has been granted by the South Metropolitan Health Service (SMHS) Human Research Ethics Committee (HREC), the Western Australian Department of Health HREC (for hospital and emergency data) and the Curtin University HREC. Governance has also been approved for the six hospitals and medical sites assisting with recruitment. Services Australia has also approved participant healthcare data to be accessed at the completion of the study.

All participants will be given a Participant Information Sheet and two Consent Forms (1 project consent form and 1 Services Australia consent form), with sufficient time to read it and ask questions prior to providing written consent. All participants will be required to provide written informed consent prior to participation and data collection commencing. Participants may refuse the right to participate or withdraw at any time from the research project up to the point that data are de-identified and analysed.

Data will be de-identified and participant confidentiality maintained at all times. It is expected the results will be published in peer-review journals and presentations delivered to the community, industry and at academic conferences.

## CONCLUSION

People living with MCI fall and experience fall injuries nearly twice as often as those living with no cognitive impairment [7]. To the authors' knowledge no RCTs have evaluated the effect of a balance-focused multi-modal exercise program to improve balance and prevent falls for people with MCI over the long term (i.e., 6 and 12 months). This study aims to address this current gap in the literature. We will also evaluate whether physical performance and quality of life are improved and determine whether there is a reduction in cognitive decline. Cost-effectiveness analyses will be undertaken and if effective, the results will provide governments and policy makers with an easy to administer, cost-effective community-based program that will assist people living with MCI to live independently and reduce their risk of future falls.

## ACKNOWLEDGEMENTS

Thank you to the staff who will assist with recruitment at the following hospitals: Armadale Hospital, Fremantle Hospital, Neurosciences Unit (Graylands Hospital), Rockingham Hospital, Royal Perth Hospital and Sir Charles Gairdner Hospital. Thank you also to Injury Matters and Alzheimer's Western Australia for assisting with recruitment and the research staff working on the RCT.

## REFERENCES


1. Plassman, B., et al., *Incidence of dementia and cognitive impairment, not dementia in the United States.* Annals of Neurology, 2011. **70**(3): p. 418-426.
2. Su, X., et al., *Prevalence and predictors of mild cognitive impairment in Xi'an: a community-based study among the elders.* PLOS One, 2014. **9**(1): p. e83217.
3. Anstey, K., et al., *Characterizing mild cognitive disorders in the young-old over 8 years: prevalence, estimated incidence, stability of diagnosis, and impact on IADLs.* Alzheimer's & Dementia,, 2013. **9**(6): p. 640-648.
4. Brodaty, H., et al., *Mild cognitive impairment in a community sample: the Sydney Memory and Ageing Study.* Alzheimer's & Dementia, 2013. **9**(3): p. 310-317.
5. Chong, T., et al., *Physical activity for older Australians with mild cognitive impairment or subjective cognitive decline – A narrative review to support guideline development.* Journal of Science and Medicine in Sport, 2020. **23**: p. 913-920.
6. Winblad, B., et al., *Mild cognitive impairment - beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment.* Journal of Internal Medicine & Health, 2004. **256**(3): p. 240-246.
7. Delbaere, K., et al., *Mild cognitive impairment as a predictor of falls in community dwelling older people.* The American Journal of Geriatric Psychiatry, 2012. **20**(10): p. 845-853.
8. AIHW: Bradley, C., *Hospitalisations due to falls by older people, Australia 2007–08. Injury research and statistics series no. 61. Cat. no. INJCAT 137.* . 2012, AIHW: Canberra.
9. AIHW: Pointer, S., *Trends in hospitalised injury, Australia 1990-00 to 2012-13. Injury research and statistics series no. 95. Cat. no. INJCAT 171*. 2015, AIHW: Canberra.
10. AIHW: Pointer, S., *Trends in hospitalised injury due to falls in older people, 2002–03 to 2014–15. Injury research and statistics series no. 111. Cat. no. INJCAT 191*. 2018, AIHW: Canberra.
11. Sherrington, C., et al., *Exercise for preventing falls in older people living in the community, Issue 1. Art. No.: CD012424.* Cochrane Database of Systematic Reviews, 2019.
12. Hagovská, M. and Z. Olekszyová, *Impact of the combination of cognitive and balance training on gait, fear and risk of falling and quality of life in seniors with mild cognitive impairment.* Geriatrics and Gerontology International, 2016. **16**(9): p. 1043-1050.
13. Huang, N., et al., *Effects of a Modified Tai Chi program on older people with mild Dementia: A randomized controlled trial.* Journal of Alzheimer's Disease, 2019. **72**(3): p. 947-956.
14. Mirelman, A., et al., *Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial.* Lancet Infectious Diseases, 2016. **388**(10050): p. 1170-1182.
15. Schwenk, M., et al., *Sensor-based balance training with motion feedback in people with mild cognitive impairment.* Journal of Rehabilitation Research and Development, 2016. **53**(6): p. 945-958.
16. Sungkarat, S., et al., *Effects of Tai Chi on cognition and fall risk in older adults with mild cognitive impairment: A randomized controlled trial.* Journal of the American Geriatrics Society, 2017. **65**(4): p. 721-727.
17. World Health Organization, *WHO Guidelines on Physical Activity and Sedentary Behaviour*. 2020, World Health Organization: Geneva.
18. Lautenschlager, N., et al., *Physical Activity Guidelines for Older Australians with Mild Cognitive Impairment or Subjective Cognitive Decline*. 2018, Dementia Collaborative Research Centres: Melbourne.
19. Burton, E., et al., *Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: a systematic review and meta-analysis.* Clinical Interventions in Aging, 2015. **10**: p. 421-434.

20. Sherrington, C., et al., *Exercise to prevent falls in older adults: An updated systematic review and meta-analysis.* British Journal of Sports Medicine, 2017. **51**: p. 1749-1757.
21. Dite, W. and V. Temple, *A clinical test of stepping and change of direction to identify multiple falling older adults.* Archives of Physical Medicine and Rehabiliation, 2002. **83**(11): p. 1566-1571.
22. Guralnik, J., et al., *A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission.* Journal of Gerontology, 1994. **49**(2): p. M85-94.
23. Podsiadlo, D. and S. Richardson, *The timed up and go: A test of basic functional mobility for frail elderly persons.* Journal of American Geriatrics Society, 1991. **39**: p. 142-148.
24. Guyatt, G., et al., *The 6-minute walk: A new measure of exercise capacity in patients with chronic heart failure.* Canadian Medical Association Journal, 1985. **132**(8): p. 919-923.
25. Logsdon, R., et al., *Quality of life in Alzheimer's disease: Patient and caregiver reports.* Journal of Mental Health & Aging, 1999. **5**(1): p. 21-32.
26. Logsdon, R., et al., *Assessing quality of life in older adults with cognitive impairment.* Psychosomatic Medicine, 2002. **64**(3): p. 510-519.
27. Nasreddine, Z., et al., *The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment.* Journal of the American Geriatrics Society, 2005. **53**(4): p. 695-699.
28. Moher, D., et al., *CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**(c869).
29. Petersen, R., et al., *Mild cognitive impairment: Clinical characterisation and outcome.* Archives of Neurology, 1999. **56**(3): p. 303-308.
30. Hughes, C., et al., *A new clinical scale for the staging of dementia.* British Journal of Psychiatry, 1982. **140**: p. 566-572.
31. Folstein, M., *Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician.* Journal of Psychiatric Research, 1975. **12**: p. 189-198.
32. Almeida, O. and S. Almeida, *Short versions of the Geriatric Depression Scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV.* International Journal of Geriatric Psychiatry, 1999. **14**: p. 858-865.
33. Lamb, S., et al., *Development of a common outcome data set for fall injury prevention trials: The Prevention of Falls Network Europe Consensus.* Journal of the American Geriatrics Society, 2005. **53**(9): p. 1618-1622.
34. McKeea, K. and M. Hackney, *The Four Square Step Test in individuals with Parkinson's disease: Association with executive function and comparison with older adults.* NeuroRehabilitation, 2014. **35**: p. 279-289.
35. Fox, B., et al., *Relative and absolute reliability of functional performance measures for adults with dementia living in residential aged care.* International Psychogeriatrics, 2014. **26**(10): p. 1659-1667.
36. Olsen, C. and A. Bergland, *Reliability of the Norwegian version of the short physical performance battery in older people with and without dementia.* BMC Geriatrics, 2017. **17**.
37. Washburn, R. and J. Ficker, *Physical activity scale for the elderly (PASE): The relationship with activity measured by a portable accelerometer.* Journal of Sports Medicine and Physical Fitness, 1999. **39**(4): p. 336-340.
38. Washburn, R., et al., *The physical activity scale for the elderly (PASE): Evidence for validity.* Journal of Clinical Epidemiology, 1999. **52**(7): p. 643-651.
39. Washburn, R., et al., *The physical activity scale for the elderly (PASE): Development and evaluation.* Journal of Clinical Epidemiology, 1993. **46**(2): p. 153-162.

40. Campbell, A.J., et al., *Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women.* British Medical Journal, 1997. **315**: p. 1065-1069.
41. Haines, T., et al., *Patient education to prevent falls among older hospital inpatients: a randomized controlled trial.* Archives of Internal Medicine, 2011. **171**(6): p. 516-524.
42. Guralnik, J., et al., *Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery.* Journals of Gerontology: *Series A Biological Sciences & Medical Sciences*, 2000. **55**(4): p. M221-M231.
43. Klenk, J., et al., *Concurrent validity of activPAL and activPAL3 accelerometers in older adults.* Journal of Aging & Physical Activity, 2016. **24**: p. 444-450.
44. McAuley, E., et al., *Predicting long-term maintenance of physical activity in older adults.* Preventive Medicine, 2003. **37**: p. 110-118.
45. Hauer, K., et al., *Validation of the Falls Efficacy Scale and Falls Efficacy Scale International in geriatric patients with and without cognitive impairment: Results of self-report and interview-based questionnaires.* Gerontology, 2010. **56**(2): p. 190-199.
46. Lowry, M. *Clock Yourself and Balance Yourself*. 2017 [cited 2018 20 December]; Available from: http://clockyourself.com.au/balanceyourself/.
47. Blennerhassett, J. and V. Jayalath, *The Four Square Step Test is a feasible and valid clinical test of dynamic standing balance for use in ambulant people poststroke.* Archives of Physical Medicine and Rehabilitation, 2008. **89**(11): p. 2156-2161.
48. Lautenschlager, N., et al., *Effect of physical activity on cognitive function in older adults at risk for alzheimer disease: A randomized trial.* Journal of the American Medical Association, 2008. **300**(9): p. 1027-1037.
49. Easton, T., et al., *An empirical comparison of the measurement properties of the EQ-5D-5L, DEMQOL-U and DEMQOL-Proxy-U for older people in residential care.* Quality of Life Research, 2018. **27**: p. 1283-1294.
50. Drummond, M., et al., *Methods for the Economic Evaluation of Health Care Programmes*. 2015, Oxford: Oxford University Press.
51. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards.* BMJ, 2013. **346**(f1049).

## CONTRIBUTIONS

EB conceived the study, designed the final protocol, wrote the initial draft of the protocol paper and is the sole investigator of the fellowship grant. KH, NL, KE, JM, ML, AMH, helped in the design of the final study protocol and revised initial manuscript draft; AJ provided biostatistical support; RM provide health economic analyses support; KE provided outcome data support and will provide research translation support; JT, SB, CO, LB, RC, MC, SW are coordinating recruitment at each of their sites. All authors edited the manuscript and approved the final manuscript.

## FUNDING STATEMENT

This project is funded by the National Health and Medical Research Council (NHMRC) (Investigator Grant – APP1174739) and Curtin University.

## COMPETING INTERESTS STATEMENT

The authors have no competing interests.

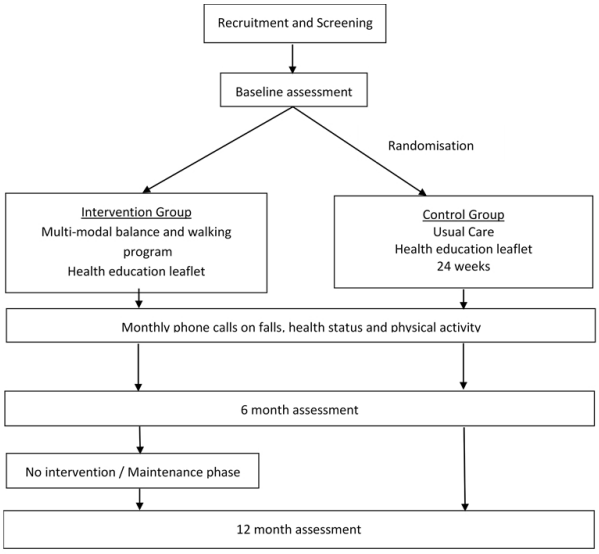


Figure 1. Study Design

338x190mm (96 x 96 DPI)

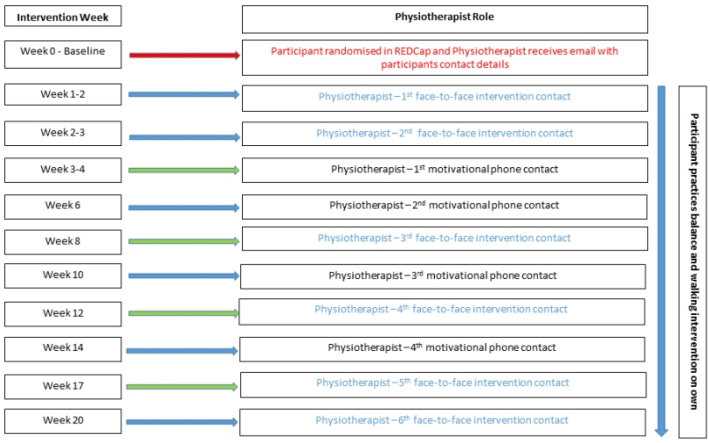


Figure 2 Timeline of intervention delivery by physiotherapists

855x481mm (38 x 38 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Yes |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Yes |
| | 2b | All items from the World Health Organization Trial Registration Data Set | NA |
| Protocol version | 3 | Date and version identifier | NA |
| Funding | 4 | Sources and types of financial, material, and other support | Yes |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Yes |
| | 5b | Name and contact information for the trial sponsor | Yes |
| | 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 | Yes |
| | 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) | NA |
| **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 | Yes |
| | 6b | Explanation for choice of comparators | |
| Objectives | 7 | Specific objectives or hypotheses | Yes |

| | | | |
|---|---|---|---|
| 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) | Yes |
| **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 | Yes |
| 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) | Yes |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Yes |
| | 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) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Yes |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Yes |
| 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 | Yes |
| 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) | Yes |
| 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 | Yes |

| | | | |
|---|---|---|---|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Yes |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | Yes |
| 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 | Yes |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Yes |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Yes |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Yes |
| | 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 | |

| | | | |
|---|---|---|---|
| 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 | Yes |
| 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 | Yes |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Yes |
| | 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) | Yes |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | Yes |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Yes |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Yes |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Yes |

| | | | |
|---|---|---|---|
| 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) | |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Yes |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| 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 | Yes |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Yes |
| 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 | Yes |
| 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 | |
| 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 | Yes |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Balance on the Brain: A randomised controlled trial evaluating the effect of a multimodal exercise program on physical performance, falls, quality of life and cognition for people with mild cognitive impairment: Study protocol

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2021-054725.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 31-Jan-2022 |
| Complete List of Authors: | Burton, Elissa; Curtin University - Perth City Campus, Curtin School of Allied Health; Curtin University, enAble Institute<br>Hill, Keith; Monash University, Rehabilitation, Ageing and Independent Living (RAIL) Research Centre, School of Primary and Allied Health Care<br>Ellis, Kathryn; University of Melbourne, The Academic Unit for Psychiatry of Old Age, Department of Psychiatry; University of Melbourne, Melbourne School of Psychological Sciences<br>Hill, Anne-Marie; The University of Western Australia, School of Allied Health, Western Australian Centre for Health and Ageing<br>Lowry, Meggen; Next Step Health<br>Moorin, Rachael; Curtin University, Curtin School of Population Health; University of Western Australia, School of Population and Global Health<br>McVeigh, Joanne; Curtin University, Curtin School of Allied Health; University of Witwatersrand, School of Physiology<br>Jacques, Angela; Curtin University, Curtin School of Allied Health<br>Erickson, Kirk; University of Pittsburgh, Center for the Neural Basis of Cognition; Murdoch University, College of Science, Health, Engineering, and Education<br>Tate, Joel; Armadale Health Service, Department of Rehabilitation and Aged Care<br>Bernard, Sarah; Sir Charles Gairdner Hospital Group, Geriatric Acute and Rehabilitation Medicine<br>Orr, Carolyn; Royal Perth Hospital, Cognitive Clinic<br>Bongiascia, Luke; Rockingham Peel Group, Physiotherapy Department, Adult Community and Allied Health Directorate<br>Clarnette, Roger; University of Western Australia, Medical School<br>Clarke, Melanie; North Metropolitan Health Service Mental Health, Public Health and Dental Services, Neurosciences Unit<br>Williams, Shannon; Royal Perth Hospital, Neurogenetic Clinic and Physiotherapy Department<br>Lautenschlager, Nicola; University of Melbourne, Academic Unit of Psychiatry of Old Age; The Royal Melbourne Hospital, NorthWestern Mental Health |
| Primary Subject Heading: | Public health |
| Secondary Subject Heading: | Rehabilitation medicine, Sports and exercise medicine |

| Keywords: | PUBLIC HEALTH, REHABILITATION MEDICINE, PREVENTIVE MEDICINE |
| --- | --- |

# Balance on the Brain: A randomised controlled trial evaluating the effect of a multimodal exercise program on physical performance, falls, quality of life and cognition for people with mild cognitive impairment: Study protocol.

**Short title:** Balance on the Brain Study Protocol

Elissa Burton[1,2], Keith D Hill[3], Kathryn A Ellis[4,5], Anne-Marie Hill[6], Meggen Lowry[7], Rachael Moorin[8,9], Joanne McVeigh[1,10], Angela Jacques[1], Kirk I. Erickson[11,12], Joel Tate[13], Sarah Bernard[14], Carolyn F Orr[15], Luke Bongiascia[16], Roger Clarnette[17], Melanie L Clark[18], Shannon Williams[19], Nicola T Lautenschlager[4,20].

[1]Curtin School of Allied Health, Faculty of Health Sciences, Curtin University, Perth, Australia

[2]enAble Institute, Faculty of Health Sciences, Curtin University, Perth, Australia

[3]Rehabilitation, Ageing and Independent Living (RAIL) Research Centre, School of Primary and Allied Health Care, Monash University, Melbourne, Australia

[4]Academic Unit for Psychiatry of Old Age, Department of Psychiatry, The University of Melbourne, Melbourne, Australia

[5]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia

[6]School of Allied Health, Western Australian Centre for Health and Ageing, The University of Western Australia, Perth, Australia

[7]Next Step Health, Brisbane, Queensland

[8]Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Perth, Australia

[9]School of Population and Global Health, The University of Western Australia, Perth, Australia

[10]Movement Physiology Laboratory, School of Physiology, University of Witwatersrand, South Africa

[11]Department of Psychology, Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, United States of America

[12]Murdoch University, College of Science, Health, Engineering, and Education, Perth, Western Australia

[13]Department of Rehabilitation and Aged Care, Armadale Health Service, Perth, Australia

[14] Geriatric Acute and Rehabilitation Medicine, Sir Charles Gairdner Hospital Group, Perth, Australia

[15]Cognitive Clinic, Royal Perth Hospital, Perth, Australia

[16]Physiotherapy Department, Adult Community and Allied Health Directorate, Rockingham Peel Group, Rockingham, Australia

[17]Medical School, University of Western Australia, Crawley, Australia

[18]Neurosciences Unit, North Metropolitan Health Service Mental Health, Public Health and Dental Services, Perth, Australia

[19]Neurogenetic Clinic and Physiotherapy Department, Royal Perth Hospital, Perth, Australia

[20]NorthWestern Mental Health, Royal Melbourne Hospital, Australia

Corresponding Author:
Dr Elissa Burton
Senior Research Fellow
Curtin School of Allied Health
enAble Institute
Faculty of Health Sciences
Curtin University
Perth, WA, Australia
PO Box U1987
Perth WA 6845
Email: E.Burton@curtin.edu.au

**Word Count**: 5,155

**Keywords**: mild cognitive impairment, balance, exergame, falls, quality of life, cognition.

# Balance on the Brain: A randomised controlled trial evaluating the effect of a multimodal exercise program on physical performance, falls, quality of life and cognition for people with mild cognitive impairment: Study protocol.

**Short title:** Balance on the Brain Study Protocol

**Abstract:**

**Introduction**: Exercise and physical activity have been shown to improve cognition for people living with mild cognitive impairment (MCI). There is strong evidence for the benefits of aerobic exercise and medium evidence for participating in regular strength training for people with MCI. However, people living with MCI fall twice as often as those without cognitive impairment and the evidence is currently unknown as to whether balance training for people with MCI is beneficial, as has been demonstrated for older people without cognitive impairment. The aim of this study is to determine whether a balance-focused multimodal exercise intervention improves balance and reduces falls for people with MCI, compared to a control group receiving usual care.

**Methods and Analysis**: This single blind randomised controlled trial (Balance on the Brain) will be offered to 396 people with MCI living in the community. The multi-modal exercise intervention consists of two balance programs and a walking program to be delivered by physiotherapists over a 6-month intervention period. All participants will be followed up over 12 months (for the intervention group this involves 6 month intervention and 6 months maintenance). The primary outcomes are 1) balance performance and 2) rate of falls. Physical performance, levels of physical activity and sedentary behaviour, quality of life and cognition are secondary outcomes. A health economic analysis will be undertaken to evaluate the cost effectiveness of the intervention compared with usual care.

**Ethics and Dissemination**: Ethics approval has been received from the South Metropolitan Health Service (SMHS) Human Research Ethics Committee (HREC), Curtin University HREC, and the Western Australia Department of Health HREC; and approval has been received to obtain data for health costings from Services Australia. The results will be disseminated through peer-review publications, conference presentations, and on-line platforms.

**Registration Details**: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620001037998.

**Keywords**: mild cognitive impairment, balance, exergame, falls, quality of life, cognition.

## Strengths and Limitations of this Study

- To our knowledge this is the first randomised controlled trial for people living with MCI that will evaluate the effect of exercise on improving balance and reducing falls.
- An economic evaluation from a healthcare perspective allows for potential future implementation should the intervention be effective.
- Participants will be monitored regularly with monthly follow-up phone calls collecting physical activity, health and falls data.
- The study is statistically powered for both primary outcomes (i.e. balance and falls), baseline and outcome assessors are blinded to group allocation.
- A limitation may be convenience sampling (i.e. one state) rather than population-based sampling (i.e. multi-state) which may not be representative of the Australian MCI population.

## INTRODUCTION

The prevalence of mild cognitive impairment (MCI) varies between 20% for those aged 70+ years in USA,[1] 12.2-15.5% in China for those aged 55 and 60 and over respectively,[2, 3] between 6.8-22.5% in Latin America and Caribbean populations over 50 years of age, [4] up to 37% for Australians aged 70-90 years [5] and leads to an increased risk of dementia.[6] According to the International Working Group on MCI the core features of MCI include: evidence of deterioration in cognition either objectively measured over time and/or through self-report or by an informant reporting cognitive deficits beyond that expected for age and education level; the person not presenting with dementia; and activities of daily living being preserved, although there may be some mild impairment in complex activities.[7, 8]

People with MCI are more likely to fall than those of the same age without cognitive impairment.[9] This is often due to a decrease in motor function and balance, which may be associated with age-related change in white matter.[10] MCI can also affect specific gait parameters, and falls risk is increased particularly when a person with MCI is cognitively challenged or during dual-tasking.[11, 12] The average age of the population is also increasing, therefore MCI and falls are likely to affect thousands more people, including Australians as they age. This will not only negatively affect individuals and their families but will have a significant impact on health budgets over the coming decades unless successful interventions are developed and implemented widely (i.e. Australian falls-related costs estimated at $648 million in 2007-2008,[13] and falls are the leading cause of injury-related hospitalisations in Australia,[14] with age standardised rates increasing at >2% per annum).[15]

For older people living in the community without cognitive impairment, balance exercise programs that mainly contain balance and functional training components have been shown to be one of the most effective measures for decreasing the risk and rate of falling.[16] Balance exercises may also benefit people living with MCI however, the current evidence is less clear. Eight randomised controlled trials [17-24] have been conducted with people with MCI which have included measuring falls or fear of falling, however none have specifically used a balance exercise program, nor followed participants for a long period of time (up to12 months) with falls being the primary outcome.

Recently developed physical activity guidelines for older Australians with MCI or subjective cognitive decline (SCD),[25] recommended the same amount of aerobic, strength and balance exercise per week as the guidelines for all older adults (i.e. 150 minutes moderate intensity aerobic activity, plus two strength and balance sessions per week [26]). The evidence for participating in aerobic activity is strong for people living with MCI and shows significant

benefits to their brain health and function. [25] However, there is a lack of evidence to make specific recommendations for this population on balance recommendations.[7, 25] The guidelines noted there were no research trials specifically examining balance interventions in older adults with MCI and subjective cognitive decline and therefore their current recommendations were extrapolated from studies of older adults with no cognitive impairment.[25] A systematic review by Burton et al.[27] also showed few balance interventions have been undertaken to reduce falls for people living with dementia. Maintaining balance as one ages is critical for participating in everyday activities, staying mobile, living independently and reducing the risk of falling.[28]

Despite a number of additional randomised controlled trials evaluating exercise interventions in people with MCI since the publication of these recommendations, there remains a gap in the research and a critical need to better understand whether balance can be improved for people with MCI living in the community and if so, whether improved balance is translated into fewer falls. This project provides an opportunity to address these important research gaps and assist people with MCI, their caregivers, healthcare providers and potentially reduce the cost of healthcare into the future.

The aims of this research are to determine whether a balance-focused multimodal exercise intervention improves balance and reduces the rate of falls for people with MCI, compared to a control group (receiving usual care and a health promotion flyer). The study also aims to evaluate the cost effectiveness of the intervention compared with usual care. Secondary aims include evaluating the effect of the intervention on physical performance, falls efficacy and quality of life and reducing cognitive decline.

It is hypothesised that older adults with MCI participating in the balance-focused multimodal exercise intervention, when compared to the usual care group (control), will (during the intervention and for the following 6 months) achieve:

a. improved balance (improvement on 4-square step test [29]);
b. a decrease in falls rate (using monthly calendar and phone calls) and improved falls efficacy (improvement on Falls Efficacy Scale – International [30]);
c. improved physical performance (improvement in the Short Physical Performance Battery (SPPB),[31] Timed-Up-And-Go (TUG),[32] 6 minute walk test (6MWT) [33]) and physical activity (increase in step count using activPAL4 accelerometers);
d. improved quality of life (improvement on Quality of Life – Alzheimer's Disease (QOL-AD) [34, 35];
e. a reduction in rate of cognitive decline (Montreal Cognitive Assessment (MoCA)[36]).

It is also hypothesised that the exercise program will be cost-effective compared with usual care, defined as having an incremental cost-effectiveness ratio of less than $50,000/QALY gained. In addition, the cost per fall per will be evaluated.

## METHODS AND ANALYSIS

### Study Design

This will be a single blind randomised controlled trial (RCT), comparing a balance-focused multimodal exercise intervention to a usual care control group for people with MCI (see Figure 1). The CONSORT statement [37] has been used as a framework for developing the project methodology. The study recruitment and data collection will be undertaken from the start of 2021 through to the end of 2024.

### Participants

Three hundred and ninety-six participants living with MCI will be recruited across the Perth and Rockingham metropolitan areas of Western Australia. Participants will be included if they meet the following criteria: aged over 50 years; living in the community with a diagnosis of MCI consistent with the Petersen criteria,[38] including self-reported memory complaint, a Clinical Dementia Rating [39] (CDR) of 0.5; and Standardised Mini-Mental Status Examination [40] (SMMSE) score of 24 or above. Other inclusion criteria are: not meeting Australian physical activity guidelines (i.e.<150 minutes of moderate intensity physical activity a week self-reported) and not participating in balance training regularly (i.e.< twice a week).

Participants will be excluded if they have an unstable medical condition, terminal illness, diagnosis of significant cognitive impairment and/or chronic mental illness (e.g. schizophrenia), severe sensory impairment affecting mobility, live in residential aged care, drink more than 4 standard alcoholic drinks per day (i.e. >28/week), score >6 for the Geriatric Depression Scale-15 item (GDS-15) [41] or have a lack of fluency in written and spoken English.

### Recruitment and Screening

Participants will be recruited from the community via 9 memory cafes that are held throughout Perth and organised by Alzheimer's Western Australia (WA), advertisements in the local media including CurtinFM radio, The Senior and Have a Go newspapers, and where possible through news segments on television. Alzheimer's WA will also forward enquiries from people with MCI who wish to participate. A Facebook page providing up to date information about the

project will be developed and advertisements sent out promoting the study. Memory clinics at Armadale Hospital, Fremantle Hospital, and Sir Charles Gairdner Hospital, the Royal Perth Cognitive Disorder Clinic, the Aged Care Rehabilitation clinics, at Rockingham General Hospital, the Aged Care Assessment Team (ACAT), the Regional Assessment Service (RAS) and the Neurosciences Unit will all assist with recruitment.

The research team will contact potential participants by telephone to check the suitability of the person in accordance with the inclusion and exclusion criteria using a screening protocol. The telephone screen includes a description of the study, questions about memory, current physical activity levels, living situation, availability over the following 6 month period, cognitive screen (i.e. TICS-M), health screening (i.e., vision, hearing, medical conditions), alcohol consumption, not participating in drug trials and the GDS-15. The GDS-15 is included in the screening to determine the presence of clinically relevant symptoms of depression. If the participant reports a medical diagnosis of depression they will not be required to complete the GDS-15. The full phone screening tool is available from the corresponding author and takes approximately 45 minutes to complete. The contact details of the participant and their general practitioner will also be collected.

To complete the screening process the Research Officer will meet with the potential participant face-to-face at a location comfortable for both parties and complete the questions required to determine a diagnosis of MCI for this study (see inclusion criteria). This includes a self-reported memory complaint, completing the CDR and receiving a score of 0.5 and the SMMSE with a score of ≥24, or diagnosis from medical specialist (e.g. Geriatrician, Neurologist). If these criteria are met, participants will be asked if they have read the Participant Information Sheet and Consent Form (if not they will be asked to read it then) and have any questions about participation in the trial answered. Prior to commencing in the study each participant will provide written consent.

**Outcomes and Assessments**

An overview of the primary and secondary outcomes and assessment tools to measure each outcome are presented in Table 1. All assessments are valid, reliable and have been trialled with people with MCI. Participants will be closely supervised during all balance and mobility assessment tasks, as is routine practice when using these assessment items. To ensure standardisation of procedures, the Research Officers collecting the data will be trained by the same Chief Investigator who has a background in exercise science.

All participants will be assessed at baseline, six months (i.e., completion of the intervention period) and 12 months. This study will have two primary outcomes:

1) balance: measured using the four square step test
2) falls rate: measured using monthly calendars and follow-up phone call. A fall will be defined as “an unexpected event in which the individual comes to rest on the ground, floor or lower level” [42] as recommended by the Prevention of Falls Network Europe.

**Table 1 Assessments and timelines for Balance on the Brain**

| Measure | Outcome (Primary / Secondary) | Phone / Home Screen | Baseline | 6 Months | 12 Months |
|---|---|---|---|---|---|
| Geriatric Depression Scale – 15 Item | | X | | | |
| Modified Telephone Interview for Cognitive Status (TICS-M) | | X | | | |
| Standardised Mini-Mental State Examination (SMMSE) | | X | | | |
| Cognitive Dementia rating (CDR) | | X | | | |
| Balance: Four Square Step Test (4SST) [29, 43] | Primary | | X | X | X |
| Primary falls: collected using a monthly call and calendar | Primary | | Monthly phone call and calendar | | |
| Physical performance: Short Physical Performance Battery (SPPB) Test [31, 44, 45] | Secondary | | X | X | X |
| Physical performance: Timed Up and Go (TUG) Test [32] | Secondary | | X | X | X |
| Physical performance: 6 Minute Walk Test (6MWT) [33] | Secondary | | X | X | X |
| Physical activity: Accelerometer worn for 7 days (ActivPAL4) (step count and time spent in moderate to vigorous physical activity) | Secondary | | X | X | X |
| Physical activity: Physical Activity Scale for the Elderly (PASE) administered a week after each assessment (at accelerometer pick up) [46-48] | Secondary | | X + 1 week | X + 1 week | X + 1 week |

| | | | | | |
|---|---|---|---|---|---|
| Quality of Life: Quality of Life – Alzheimer's Disease (QOL-AD) [34, 35] | Secondary | | X | X | X |
| Cognition: Montreal Cognitive Assessment (MOCA) Test [36] | Secondary | | X | X | X |
| Secondary falls: number of fallers, injurious falls | Secondary | | Monthly phone call and calendar | | |
| Falls efficacy: Falls Efficacy Scale – International (FES-I) [30] | Secondary | | X | X | X |

*Note.* An injurious fall will be defined as a fall where the participant sought "medical advice." Data will also be collected on any injury sustained such as bruising, laceration, fracture, loss of consciousness or if the participant reports ongoing pain.[49, 50]

The four square step test (dynamic standing balance) uses four walking sticks/poles/pvc pipes to create four squares (i.e. quadrants).[29] To complete the test the participant steps both feet into each quadrant in a clockwise direction, then in an anti-clockwise direction back to the starting position, without touching the poles.[29] Two full trials are completed and the fastest time is reported.

All study participants will be asked to complete a monthly calendar that includes falls information (i.e., fall and date occurred), changes to health and self-reported physical activity. This will be followed up each month with a phone call to collect these data (i.e., falls, changes to health, physical activity). At each monthly call participants will be reminded to keep their calendar in a place they view often, as a reminder to complete it and will also be asked if they had any falls not recorded in the calendar. Falls data collected during the phone call will include number of falls, where they occurred, injuries, medical attention required etc.

The SPPB groups a number of physical performance measures such as gait speed, chair stand and balance tests into one test.[51] It has been used to monitor function in older people and those with MCI as well as predict possible disability, risk for mortality and residential aged care admission. Scores range from 0 (worst performance) to 12 (best performance).

The TUG test is used to measure a person's mobility but also includes the ability to stand up from a chair, walk three metres, turn, walk back and sit down in the chair.[32] The participant will be timed using a stop watch. Each participant will be given a practice trial that is not timed and then asked to complete the TUG.

The 6 minute walk test (6MWT) is a sub-maximal exercise test used to assess walking endurance and aerobic capacity.[33] Participants will walk around a circuit which is at least 12

metres long for 6-minutes with the distance calculated at the end of this time. The circuit will be marked by using bright coloured cones.

Physical activity will be measured using ActivPAL4™ accelerometers. The activPAL™ is currently considered the most accurate field-based measure of sitting time and sit-to-stand transitions.[52] The accelerometers will be worn, and data collected over a 7 day period at baseline, 6 and 12 month data collection. ActivPAL™ data will be converted to event level files using propriety PAL Technologies software. The following variables will be derived from the accelerometer data across the 7 days: step count, time spent in sedentary, upright and stepping activities, stepping intensity (cadence), and duration of lying, sitting, standing and stepping activities. The activPAL4™ will be worn on the thigh, is waterproof and does not need to be removed for the 7 days. The accelerometer will be applied by research staff using a Tegaderm dressing and removed by the research staff on return. Each device is small (23.5mm x 43mm x 5mm) and weighs 9 grams.

The Physical Activity Scale for the Elderly (PASE) is a 12-item self-report instrument designed to assess physical activity levels in older people over a 1-week period.[46] It combines physical activity information during leisure, household, and occupational activity.[53] A score is calculated based on activity frequency and an activity-weighted score multiplied by frequency.[48] The higher the PASE score, the more physically active a person is, with PASE scores ranging from zero to 400.

The Quality of Life in Alzheimer's Disease (QOL-AD) tool is a 13-item measure designed to obtain a rating of quality of life.[34, 35] Each question is rated on a four point scale, 1 being poor and 4 being excellent, total scores range between 13-52.[34, 35] It was specifically designed for people with cognitive impairment.

Cognition will be assessed using the Montreal Cognitive Assessment (MoCA), which assesses eight cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation.[36] The total maximum score is 30 points and the research staff will administer it face to face.[36]

The Falls Efficacy Scale – International (FES-I) is a 16-item tool used to measure "concerns about falling" and is recommended to be administered face-to-face for people with cognitive impairment.[54] Participants will be asked to answer each question on a Likert scale from "not at all concerned" (1) through to "very concerned" (4), based on whether they think they would be concerned about falling while participating in the activities, e.g. *How concerned are you about falling while cleaning the house (e.g. sweeping, vacuuming, or dusting)?*

## Randomisation and Blinding

A concealed, computer-generated sequence of randomly selected permuted blocks (block size = 6) in a 1:1 ratio will be generated by a statistician not involved in the study. A staff member (external to the study) from Curtin University's Clinical Trials Data Management Centre will enter the randomisation codes into the REDCap project data management system, minimising bias by concealing randomisation. Once a participant has been recruited and they provide written consent to participate, baseline data collection will be undertaken by one of three Research Officer staff. After baseline data collection is completed and has been entered into REDCap by a Research Officer the lead researcher will then press the randomisation button (which will allocate that participant to the intervention or control group). An email will be automatically sent by the REDCap project system (for intervention participants only) to the lead researcher (independent, not involved in assessments or intervention) who will allocate the intervention participant to a physiotherapist delivering the intervention. This email will include the contact details (i.e., name, phone number and address) of the participant allocated to the intervention group, to allow the physiotherapist to contact them directly.

The Research Officers who enrol the participants, collect and enter baseline, 6 and 12 month data will be blinded to group allocation throughout the study (Figure 1). Those delivering the intervention (i.e., physiotherapists) will not be involved in any study outcome data collection after randomisation has occurred (except for the process evaluation of the intervention delivery – separate study, methods not reported in this paper). Participants cannot be fully blinded to receiving the intervention. Participants will be reminded at each outcome assessment (i.e., baseline, 6 months and 12 months) not to divulge their group assignment to research staff or other participants (i.e., who may attend the same memory café).

*Insert Here* **[Figure 1. Study Design]**

## Intervention

The intervention period will be 24 weeks and the data collection/follow-up periods 6 and 12 months post baseline. The intervention will be delivered by qualified physiotherapists, with a background in working with older adults and those living with cognitive impairment. The physiotherapists will also complete two half-days of training prior to delivering the intervention. The balance-focused multimodal exercise intervention group will participate in the Balance Yourself (a book) [55] and Clock Yourself Programs (exergame App or CD) [55] and in

discussion with the physiotherapist progress (where appropriate) to walking 30 minutes per day, five days a week in a safe environment. Both balance programs are safe and have been delivered by experienced physiotherapists for over five years to approximately 500 older adults, including some individuals with stroke, Parkinson's Disease, MCI or early-stage dementia. These complementary programs aim to build a person's capacity to prevent falls. The Balance Yourself program aims to improve balance, whereas the Clock Yourself program aims to improve stepping reactions in all directions in the event that a person should lose their balance. Each program starts slowly and progresses over time through levels of increasing difficulty in accordance with each participants' ability. The Balance Yourself book, which has been adjusted specifically for people with MCI, guides the user to practise evidence-based balance exercises which are introduced in a progressively challenging sequence. The standing balance exercises involve standing still, and are progressed in difficulty with narrowing foot positions and then introducing head movements, reaching outside the base of support, closing eyes and dual tasking. The dynamic balance exercises involve stepping or walking in various directions and with narrowing foot positions e.g. sideways, backwards, tandem, figure of 8.

The Clock Yourself program is presented as a brain game to help people think faster on their feet. It is a volitional stepping method designed to progressively improve physical agility and stepping reaction times while a person's attention is divided. The program is deliverable by either an app (low-tech) or a set of audio CDs (no-tech). To cater for heterogeneity in tech-literacy and to promote self-efficacy with the exercise, participants can choose whichever tool they are most confident with. A guidebook is also available to assist participants to navigate the app or the CDs. Participants will be asked to progress throughout the 24-week intervention to participating in 60 minutes of the Balance Yourself program and Clock Yourself program per week, for a total of 120 minutes of balance exercise per week (i.e., 20 minutes per day). Where required, carers will be asked to support the participants to carry out the exercise programs e.g., guiding them with safe set up or providing reminders.

The walking component will be individually tailored to each participants' abilities, with emphasis on walking environments to maximise safety. Participants will be encouraged to progress to walking 30 minutes a day, 5 times a week over the 24-week intervention.

The physiotherapists will deliver the intervention approximately 7-10 days after group allocation (i.e., to intervention group), they will return for further home visits in weeks 2, 8, 12, 17 and 20 of the intervention to provide advice on technique, use of the intervention tools and progressing through the levels of exercise. Motivational phone calls will be made by the physiotherapist in weeks 3, 6, 10, and 14 of the intervention. (See Figure 2). These phone calls will include progress of the participant since the last home visit, problem solving should

any issues arise, questions on confidence of the participant to increase and/or progress activities, and any assistance they may need. Each intervention participant will be asked to practice the balance and walking programs progressing over time to 5-7 days a week (or up to 120 minutes for the week for the balance programs, plus a minimum of 30 minutes per day walking).

*Insert Here* **[Figure 2. Timeline of intervention delivery by physiotherapists]**

**Control Group**

The usual care group will receive a health promotion education leaflet, after completing baseline data collection. This will include documentation on the current physical activity recommendations for people with MCI and healthy eating and drinking recommendations. The intervention group will also receive the same education leaflet.

**Sample Size**

The sample size was calculated separately for the two primary outcomes: 1) balance, based on the four square step test) and 2) falls rate. The sample size for the balance outcome was calculated based on detecting a minimum effect size difference of 0.18 [56] over 3 time points between intervention and control groups, with 80% power and alpha=0.05. After assuming a 20% withdrawal rate over the 24 week intervention, and a further 15% loss to follow up over the following 6-month follow-up, consistent with other similar studies[57] a total of 212 participants (106 per group) is required.

The sample size for falls rate outcome was based on detecting a 30% minimum relative reduction in the falls rate (0.5 to 0.35) in the intervention group compared to the control group, with 80% power and alpha=0.05. After assuming a 20% withdrawal rate over the 24 week intervention, and a further 15% loss to follow up over the following 6-month follow-up, a sample size of n=396 is required (198 per group). Therefore a sample size of 396 participants will be required for the overall study (G*Power 3.1.9.2).

**Statistical Analysis**

Continuous data will be summarised as means and standard deviations or medians and interquartile ranges and compared using t-tests or Mann-Whitney U tests, depending on normality. Categorical data will be summarised using frequency distributions and compared using $\chi^2$ tests. The primary outcomes will be analysed at baseline, 6 and 12 months using

generalised linear mixed-effects models which use Maximum Likelihood Estimation methods (MLE) to account for data missing at random. Imputation methods will not be used as they lead to potential bias. The primary outcome of falls rate will be analysed using negative binomial regression, with adjustment for participant's observation time in the study and known confounding demographic factors with strong significant differences. Models will be summarised using predicted mean estimates, weighted mean differences and 95% confidence intervals. All final measures, regardless of intervention participation or compliance will be collected. Analysis will be performed on both intention-to-treat and per-protocol basis. Stata version 16.0 will be used for data analysis, with significance level set at 0.05.

**Economic Analysis**

Two forms of economic analyses will be undertaken: 1) a cost-utility analysis using the QOL-AD to assess the incremental cost of Quality adjusted life years (QALYs) gained; and 2) a cost-effectiveness analysis to assess the incremental cost per fall prevented. Both analyses will be undertaken from a healthcare system perspective

Given an RCT is being undertaken to determine the effectiveness of intervention, the economic evaluation will reflect a service substitution model without cost sharing or transfer. Costs of the program will be evaluated using prospective data collection for each participant and will include the costs associated with the intervention and outcomes using a healthcare system perspective. Program costs in addition to those for usual care will include:

- Training the physiotherapists to deliver the two balance programs (i.e. Balance Yourself and Clock Yourself) and the progressive walking program
- Physiotherapists salary to deliver the intervention
- Costs associated with outcomes for (all) participants (regardless of group) include:
    - Cost of Emergency Department (ED) visits
    - Cost of in-patient hospitalisation
    - Cost of ambulance use
    - Cost of General Practitioner (GP) and other Medicare subsidised out-of-hospital services (Medicare Benefits Scheme: MBS)
    - Cost of Pharmaceutical Benefits Scheme (PBS) medication.

Inpatient costs will be calculated using Diagnostic Related Group (DRG) based costings using the appropriate Independent Hospital Pricing Authority (IHPA) National Efficient Price Determination report. Cost of ED attendances will be based on urgency related/disposition group (derived using Episode End Status, Type of Visit, Triage, Sex, and Diagnosis Code)

and costed using Independent Hospital Pricing Authority (IHPA) National Efficient Price Determination report or cost report.

Ambulance utilisation will be costed at $986 per service. The cost of MBS services will be ascertained directly from the data (schedule fee, actual fee paid). PBS supported medication costs will be ascertained using the relevant PBS prescription charges (i.e. for general and health care card beneficiaries).

Effectiveness of the intervention will be measured using the framework of a within trial cost utility analysis using the QOL-AD mapped across to the EQ-5D-5L utility algorithm weighted for the Australian population to derive an overall index of the health state utility at each time point. Participant (i.e. intervention and controls) health state utilities will be captured at baseline, 6 and 12 months post recruitment.

An incremental cost-utility analysis will be undertaken to compare the mean incremental cost and QALY profiles for each group according to intervention status. The QALY profile for each intervention participant will be calculated using area under the curve methods. Where a significant difference occurs between the groups an incremental cost-effectiveness ratio (ICER) for QALYs gained based on utilities derived from the mapped EQ-5D-5L will be calculated.[58] Using the average costs for the intervention and the mean QALYs gained for the intervention, the incremental cost of the intervention will be compared to the control group and calculated and then plotted on a cost-effectiveness plane.[59] To estimate a distribution around costs and QALYs gained, and to calculate the confidence intervals around the ICERs to account for joint uncertainty in costs and QALYs gained, bootstrapping will be applied.[59] After conducting one-way and probabilistic sensitivity analysis incorporating all key variables, a cost-effectiveness acceptability curve will be plotted.[59] This will provide information as to whether the intervention is cost-effective, based on a decision maker's willingness to pay for each additional QALY gained (i.e. <$50,000/QALY gained).[59]

Cost effectiveness will also be estimated by utilising measurement of the change in other outcomes (e.g. falls rate, falls injuries) where a significant difference is observed between the intervention and control groups. Confidence intervals will be presented around the incremental cost effectiveness ratios (ICER) and cost effectiveness acceptability curves for varying threshold values of cost effectiveness will be presented. A 12-month time horizon will be used and a healthcare system perspective using within trial probabilities and costs will be undertaken. Assessment of the sensitivity of the results obtained to variation in measured effectiveness, healthcare resource use, intervention and usual care unit costs and participant groups will be undertaken using one-way and probabilistic sensitivity analysis, as per best practice guidelines.[60]

## Data management

All data will be collected and stored in Curtin University's REDCap data management system (redcap.curtin.edu.au) which uses a secure-socket-layer to encrypt the web transport layer with 2 step authentication (i.e., email or mobile). Anyone accessing this project database must provide a valid username, password and code at each log in. Each data entry instance into the REDCap file is logged. All other electronic data and information connected to this study will be kept in a password-protected Curtin University R-Drive folder only accessible by the Chief Investigators and research staff.

## Data Monitoring

The project will be managed by a steering committee that includes the Chief investigators and representatives of the Associate Investigators/Advisory Group. The steering committee will monitor (including audits) the conduct and progress of the research project and ensure that project milestones are being met; study procedures are being adhered to; data entered accurately (checking paper to electronic data) and provide guidance about the project implementation. The committee will meet and report half-yearly throughout the project. The committee will report to the appointed hospital representatives and the Ethics Committee Chairs where required. A Data Monitoring Committee (DMC) external to the study investigators will be formed and the committee will receive updates every six-months (or earlier if applicable). The aim of the DMC is to safeguard the interests of the study participants and assess the safety and integrity of the intervention. The DMC will include a person with previous experience serving on a DMC and an experienced physiotherapist and/or researcher.

## Harms

Adverse events will be documented across the 6 month intervention either by physiotherapists during intervention visits/phone calls or by research staff during monthly follow up calls to participants to collect data about adverse events, possible falls and health issues from the preceding month documented in monthly calendars. Any significant adverse events will be reported to the Human Research Ethics Committee.

## Patient and Public Involvement Statement

Two consumer representatives living with memory issues have been involved with the project since it was funded. They have assisted with the language in the Participant Information and Consent Forms and all documentation that will be read or received by the Balance on the Brain participants. They have also provided feedback on completing the monthly calendar and will continue to provide their expertise and feedback across the duration of the project.

## ETHICS AND DISSEMINATION

Ethics approval for this study has been granted by the South Metropolitan Health Service (SMHS) Human Research Ethics Committee (HREC), the Western Australian Department of Health HREC (for hospital and emergency data) and the Curtin University HREC. Governance has also been approved for the six hospitals and medical sites assisting with recruitment. Services Australia has also approved participant healthcare data to be accessed at the completion of the study.

All participants will be given a Participant Information Sheet and two Consent Forms (1 project consent form and 1 Services Australia consent form), with sufficient time to read it and ask questions prior to providing written consent. All participants will be required to provide written informed consent prior to participation and data collection commencing. Participants may refuse the right to participate or withdraw at any time from the research project up to the point that data are de-identified and analysed.

Data will be de-identified and participant confidentiality maintained at all times. It is expected the results will be published in peer-review journals and presentations delivered to the community, industry and at academic conferences.

## CONCLUSION

People living with MCI fall and experience fall injuries nearly twice as often as those living with no cognitive impairment [9]. To the authors' knowledge no RCTs have evaluated the effect of a balance-focused multi-modal exercise program to improve balance and prevent falls for people with MCI over the long term (i.e., 6 and 12 months). This study aims to address this current gap in the literature. We will also evaluate whether physical performance and quality of life are improved and determine whether there is a reduction in cognitive decline. Cost-effectiveness analyses will be undertaken and if effective, the results will provide governments and policy makers with an easy to administer, cost-effective community-based program that will assist people living with MCI to live independently and reduce their risk of future falls.

## ACKNOWLEDGEMENTS

Thank you to the staff who will assist with recruitment at the following hospitals: Armadale Hospital, Fremantle Hospital, Neurosciences Unit (Graylands Hospital), Rockingham Hospital, Royal Perth Hospital and Sir Charles Gairdner Hospital. Thank you also to Injury Matters and Alzheimer's Western Australia for assisting with recruitment and the research staff working on the RCT.

## REFERENCES


1. Plassman, B., et al., *Incidence of dementia and cognitive impairment, not dementia in the United States.* Annals of Neurology, 2011. **70**(3): p. 418-426.
2. Jia, L., et al., *Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study.* Lancet Public Health, 2020. **5**(12): p. e661–71.
3. Lu, Y., et al., *Prevalence of mild cognitive impairment in community-dwelling Chinese populations aged over 55 years: a meta-analysis and systematic review.* BMC Geriatrics, 2021. **21**(10).
4. Ribeiro, F., A. Teixeira-Santos, and A. Leist, *The prevalence of mild cognitive impairment in Latin America and the Caribbean: a systematic review and meta-analysis.* Aging & Mental Health, 2021.
5. Anstey, K., et al., *Characterizing mild cognitive disorders in the young-old over 8 years: prevalence, estimated incidence, stability of diagnosis, and impact on IADLs.* Alzheimer's & Dementia,, 2013. **9**(6): p. 640-648.
6. Brodaty, H., et al., *Mild cognitive impairment in a community sample: the Sydney Memory and Ageing Study.* Alzheimer's & Dementia, 2013. **9**(3): p. 310-317.
7. Chong, T., et al., *Physical activity for older Australians with mild cognitive impairment or subjective cognitive decline – A narrative review to support guideline development.* Journal of Science and Medicine in Sport, 2020. **23**: p. 913-920.
8. Winblad, B., et al., *Mild cognitive impairment - beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment.* Journal of Internal Medicine & Health, 2004. **256**(3): p. 240-246.
9. Delbaere, K., et al., *Mild cognitive impairment as a predictor of falls in community dwelling older people.* The American Journal of Geriatric Psychiatry, 2012. **20**(10): p. 845-853.
10. Shin, B., et al., *Effect of mild cognitive impairment on balance.* Journal Of The Neurological Sciences, 2011. **305**(1-2): p. 121-125.
11. Ansai, J., et al., *Risk factors for falls in older adults with Mild Cognitive Impairment and Mild Alzheimer Disease.* Journal of Geriatric Physical Therapy, 2019. **42**(3): p. E116-E121.
12. Bahureksa, L., et al., *The impact of Mild Cognitive Impairment on gait and balance: A systematic review and meta-analysis of studies using instrumented assessment.* Gerontology, 2017. **63**(1): p. 67-83.

13. AIHW: Bradley, C., *Hospitalisations due to falls by older people, Australia 2007–08. Injury research and statistics series no. 61. Cat. no. INJCAT 137.* . 2012, AIHW: Canberra.
14. AIHW: Pointer, S., *Trends in hospitalised injury, Australia 1990-00 to 2012-13. Injury research and statistics series no. 95. Cat. no. INJCAT 171*. 2015, AIHW: Canberra.
15. AIHW: Pointer, S., *Trends in hospitalised injury due to falls in older people, 2002–03 to 2014–15. Injury research and statistics series no. 111. Cat. no. INJCAT 191*. 2018, AIHW: Canberra.
16. Sherrington, C., et al., *Exercise for preventing falls in older people living in the community, Issue 1. Art. No.: CD012424.* Cochrane Database of Systematic Reviews, 2019.
17. Del Din, S., et al., *Falls risk in relation to activity exposure in high-risk older adults.* The Journals of Gerontology: Series A, 2020. **75**(6): p. 1198-1205.
18. Hagovská, M. and Z. Olekszyová, *Impact of the combination of cognitive and balance training on gait, fear and risk of falling and quality of life in seniors with mild cognitive impairment.* Geriatrics and Gerontology International, 2016. **16**(9): p. 1043-1050.
19. Huang, Y., et al., *The health literacy questionnaire among the aged in Changsha, China: confirmatory factor analysis.* BMC Public Health, 2019. **19**(1220).
20. Lipardo, D. and W. Tsang, *Effects of combined physical and cognitive training on fall prevention and risk reduction in older persons with mild cognitive impairment: a randomized controlled study.* Clinical Rehabilitation, 2020. **34**(6): p. 773-782.
21. Mirelman, A., et al., *Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial.* Lancet Infectious Diseases, 2016. **388**(10050): p. 1170-1182.
22. Montero-Odasso, M., et al., *Donepezil for gait and falls in mild cognitive impairment: A randomized controlled trial.* European Journal of Neurology, 2019. **26**(4): p. 651-659.
23. Schwenk, M., et al., *Sensor-based balance training with motion feedback in people with mild cognitive impairment.* Journal of Rehabilitation Research and Development, 2016. **53**(6): p. 945-958.
24. Sungkarat, S., et al., *Effects of Tai Chi on cognition and fall risk in older adults with mild cognitive impairment: A randomized controlled trial.* Journal of the American Geriatrics Society, 2017. **65**(4): p. 721-727.
25. Lautenschlager, N., et al., *Physical Activity Guidelines for Older Australians with Mild Cognitive Impairment or Subjective Cognitive Decline*. 2018, Dementia Collaborative Research Centres: Melbourne.

26. World Health Organization, *WHO Guidelines on Physical Activity and Sedentary Behaviour*. 2020, World Health Organization: Geneva.
27. Burton, E., et al., *Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: a systematic review and meta-analysis.* Clinical Interventions in Aging, 2015. **10**: p. 421-434.
28. Sherrington, C., et al., *Exercise to prevent falls in older adults: An updated systematic review and meta-analysis.* British Journal of Sports Medicine, 2017. **51**: p. 1749-1757.
29. Dite, W. and V. Temple, *A clinical test of stepping and change of direction to identify multiple falling older adults.* Archives of Physical Medicine and Rehabiliation, 2002. **83**(11): p. 1566-1571.
30. Yardley, L., *Development and initial validation of the falls efficacy scale-international (FES-I).* Age and Ageing, 2005. **34**(6): p. 614-619.
31. Guralnik, J., et al., *A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission.* Journal of Gerontology, 1994. **49**(2): p. M85-94.
32. Podsiadlo, D. and S. Richardson, *The timed up and go: A test of basic functional mobility for frail elderly persons.* Journal of American Geriatrics Society, 1991. **39**: p. 142-148.
33. Guyatt, G., et al., *The 6-minute walk: A new measure of exercise capacity in patients with chronic heart failure.* Canadian Medical Association Journal, 1985. **132**(8): p. 919-923.
34. Logsdon, R., et al., *Quality of life in Alzheimer's disease: Patient and caregiver reports.* Journal of Mental Health & Aging, 1999. **5**(1): p. 21-32.
35. Logsdon, R., et al., *Assessing quality of life in older adults with cognitive impairment.* Psychosomatic Medicine, 2002. **64**(3): p. 510-519.
36. Nasreddine, Z., et al., *The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment.* Journal of the American Geriatrics Society, 2005. **53**(4): p. 695-699.
37. Moher, D., et al., *CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**(c869).
38. Petersen, R., et al., *Mild cognitive impairment: Clinical characterisation and outcome.* Archives of Neurology, 1999. **56**(3): p. 303-308.
39. Hughes, C., et al., *A new clinical scale for the staging of dementia.* British Journal of Psychiatry, 1982. **140**: p. 566-572.
40. Folstein, M., *Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician.* Journal of Psychiatric Research, 1975. **12**: p. 189-198.

41. Almeida, O. and S. Almeida, *Short versions of the Geriatric Depression Scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV.* International Journal of Geriatric Psychiatry, 1999. **14**: p. 858-865.
42. Lamb, S., et al., *Development of a common outcome data set for fall injury prevention trials: The Prevention of Falls Network Europe Consensus.* Journal of the American Geriatrics Society, 2005. **53**(9): p. 1618-1622.
43. McKeea, K. and M. Hackney, *The Four Square Step Test in individuals with Parkinson's disease: Association with executive function and comparison with older adults.* NeuroRehabilitation, 2014. **35**: p. 279-289.
44. Fox, B., et al., *Relative and absolute reliability of functional performance measures for adults with dementia living in residential aged care.* International Psychogeriatrics, 2014. **26**(10): p. 1659-1667.
45. Olsen, C. and A. Bergland, *Reliability of the Norwegian version of the short physical performance battery in older people with and without dementia.* BMC Geriatrics, 2017. **17**.
46. Washburn, R. and J. Ficker, *Physical activity scale for the elderly (PASE): The relationship with activity measured by a portable accelerometer.* Journal of Sports Medicine and Physical Fitness, 1999. **39**(4): p. 336-340.
47. Washburn, R., et al., *The physical activity scale for the elderly (PASE): Evidence for validity.* Journal of Clinical Epidemiology, 1999. **52**(7): p. 643-651.
48. Washburn, R., et al., *The physical activity scale for the elderly (PASE): Development and evaluation.* Journal of Clinical Epidemiology, 1993. **46**(2): p. 153-162.
49. Campbell, A.J., et al., *Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women.* British Medical Journal, 1997. **315**: p. 1065-1069.
50. Haines, T., et al., *Patient education to prevent falls among older hospital inpatients: a randomized controlled trial.* Archives of Internal Medicine, 2011. **171**(6): p. 516-524.
51. Guralnik, J., et al., *Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery.* Journals of Gerontology: *Series A Biological Sciences & Medical Sciences*, 2000. **55**(4): p. M221-M231.
52. Klenk, J., et al., *Concurrent validity of activPAL and activPAL3 accelerometers in older adults.* Journal of Aging & Physical Activity, 2016. **24**: p. 444-450.
53. McAuley, E., et al., *Predicting long-term maintenance of physical activity in older adults.* Preventive Medicine, 2003. **37**: p. 110-118.

54. Hauer, K., et al., *Validation of the Falls Efficacy Scale and Falls Efficacy Scale International in geriatric patients with and without cognitive impairment: Results of self-report and interview-based questionnaires.* Gerontology, 2010. **56**(2): p. 190-199.

55. Lowry, M. *Clock Yourself and Balance Yourself*. 2017 [cited 2018 20 December]; Available from: http://clockyourself.com.au/balanceyourself/.

56. Blennerhassett, J. and V. Jayalath, *The Four Square Step Test is a feasible and valid clinical test of dynamic standing balance for use in ambulant people poststroke.* Archives of Physical Medicine and Rehabilitation, 2008. **89**(11): p. 2156-2161.

57. Lautenschlager, N., et al., *Effect of physical activity on cognitive function in older adults at risk for alzheimer disease: A randomized trial.* Journal of the American Medical Association, 2008. **300**(9): p. 1027-1037.

58. Easton, T., et al., *An empirical comparison of the measurement properties of the EQ-5D-5L, DEMQOL-U and DEMQOL-Proxy-U for older people in residential care.* Quality of Life Research, 2018. **27**: p. 1283-1294.

59. Drummond, M., et al., *Methods for the Economic Evaluation of Health Care Programmes*. 2015, Oxford: Oxford University Press.

60. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards.* BMJ, 2013. **346**(f1049).

## CONTRIBUTIONS

EB conceived the study, designed the final protocol, wrote the initial draft of the protocol paper and is the sole investigator of the fellowship grant. KH, NL, KE, JM, ML, AMH, helped in the design of the final study protocol and revised initial manuscript draft; AJ provided biostatistical support; RM provide health economic analyses support; KE provided outcome data support and will provide research translation support; JT, SB, CO, LB, RC, MC, SW are coordinating recruitment at each of their sites. All authors edited the manuscript and approved the final manuscript.

## FUNDING STATEMENT

This project is funded by the National Health and Medical Research Council (NHMRC) (Investigator Grant – APP1174739) and Curtin University.

## COMPETING INTERESTS STATEMENT

The authors have no competing interests.

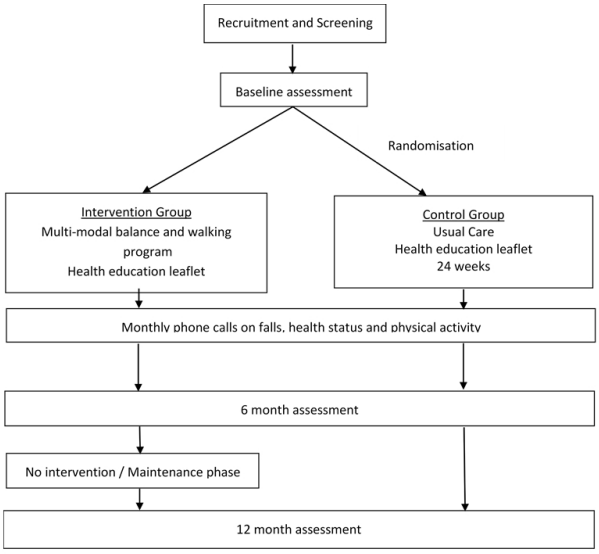


Figure 1. Study Design

338x190mm (96 x 96 DPI)

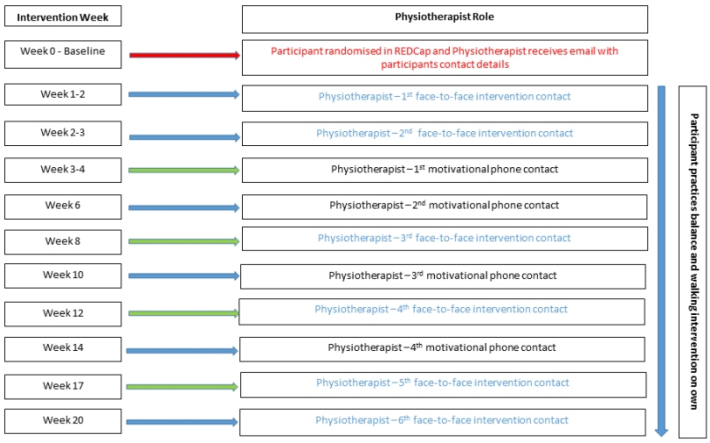


Figure 2 Timeline of intervention delivery by physiotherapists

855x481mm (38 x 38 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Page 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Page 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | NA |
| Protocol version | 3 | Date and version identifier | NA |
| Funding | 4 | Sources and types of financial, material, and other support | Page 24 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 1-2, 24 |
| | 5b | Name and contact information for the trial sponsor | NA |
| | 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 | Page 24 |
| | 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) | NA |
| **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 | Page 5-7 |
| | 6b | Explanation for choice of comparators | Page 6 |
| Objectives | 7 | Specific objectives or hypotheses | Page 6-7 |

| | | | |
|---|---|---|---|
| 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) | Page 7 |
| **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 | Page 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) | Page 7-8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Page 12-14 |
| | 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) | Page 17 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Page 12-13 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Page 8 |
| 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 | Pages 8-11 |
| 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) | Figures 1 and 2 |
| 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 | Page 14 |

| | | | |
|---|---|---|---|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 7-8 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | Page 12 |
| 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 | Page 12 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Page 12 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Page 12 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Pages 8-11 |
| | 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 | |

| | | | |
|---|---|---|---|
| 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 | Page 17 |
| 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 | Pages 14-16 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Pages 14-16 |
| | 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) | Pages 14-15 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | Page 17 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Page 17 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Page 17 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Page 18 |

| | | | |
|---|---|---|---|
| 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) | |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 8 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| 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 | Page 18 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 24 |
| 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 | Page 17 |
| 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 | |
| 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 | Page 18 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.