ARTICLE DETAILS

TITLE (PROVISIONAL)	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
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VERSION 1 – REVIEW

REVIEWER	Chan, Wayne The Hong Kong Polytechnic University, Rehabilitation Sciences
REVIEW RETURNED	22-Nov-2021

GENERAL COMMENTS	The objective of this study is to determine whether a balance-focused multimodal exercise intervention improves balance, reduces falls, and improve other physical, cognitive and psychological function for people with MCI. This study will recruit community-dwelling people with MCI who will be randomized to join either an intervention group (a balance exercise program) or a control group (usual care). Balance and incidence of falls at 6 and 12 months will be the primary outcome.
	The study protocol is generally well written and easy to follow, but some information is missing or unclear. The following is my comments and suggestions for the investigators to consider to further improve their protocol:
	Introduction:
	The authors can consider to add why balance is impaired in people with MCI, and why addressing balance impairment can reduce falls in this population. There are many risk factors contributing to falls in people with MCI, so providing more information about the association between MCI, balance and falls can strengthen the rationale of the study.
	Page 6 Line 34: Why did you choose 4-square step test as the balance measure, and use 3 different measures for physical performance?
	Methods and analysis:
	According to the guideline of BMJ Open, the date of the study should be included in the methods.
	Participants:
	Page 7 Line 24: Do you have a specific timeframe of not participating in any balance training before joining the exercise intervention?
	Outcomes and assessments:
	Page 10 Line 25: Do you have any measures to accommodate the

memory deficits of the participants (e.g., they may forget to jot down the falls information in the falls calendar and they are unable to recall afterwards)?

Page 11 Line 39: the use of FES-I was not mentioned in the study objectives and hypothesis. This should be added.

Intervention:

Page 13 Line 28: Can you explain why a walking component has been included in the exercise intervention? What is the additional use of walking exercise if the aim of this study is to evaluate the effects of a balance exercise program?

Page 13 Line 38: Apart from prescribing the exercise intervention, do you have any strategy to increase the physical activity of the participants? I'm asking because "motivational" phone calls will be made during the course of the intervention but the investigators did not mentioned what will be done in the phone calls.

REVIEWER	Ji, Yan
	Nanjing Medical University
REVIEW RETURNED	15-Dec-2021

GENERAL COMMENTS	Thank you for the opportunity to review this paper. This protocol offers a system of rules that explain the correct conduct and procedures of a randomized controlled trial for people living with MCI to evaluate the effect of exercise on improving balance and reducing falls. It would be helpful to know if balance-focused multimodal exercise intervention, which can be organized and performed easily, would benefit people with MCI. While this paper is well-structured and detailed, aspects of the paper can be improved with greater clarity.
	1. The authors identified prevalences of MCI in different areas. It would also be valuable to give a comprehensive description of the ponderance about MCI. However, some data is outdated. I conducted a brief literature search and identified a few recently published works (you might find more):
	Jia, L., Du, Y., Chu, L., Zhang, Z., Li, F., Lyu, D., . . . Group, C. (2020). 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, 5(12), e661-e671. doi:10.1016/S2468-2667(20)30185-7
	2. The text could use a comprehensive revision for literary expression.
	3. It is unclear that how the study adjusts confounding factors. Considering the complexity of falling, I would not recommend it as the primary outcome.
	4. The protocol uses two kinds of cognition assessment measurements: Standardised Mini-Mental State Examination (SMMSE) in the screening process and Montreal Cognitive Assessment (MOCA) Test in the outcome assessment process. Please explain the reason for the inconsistency.
	5. The protocol does not make a strategy to reduce withdrawal. I recommend you offer the allowance to participants at each intervention stage, or you can take other ways to enhance the adherence.
	6. In the "Outcomes and Assessments" section, the authors had

	better summarize the secondary outcomes.
	7. In "Randomisation and Blinding", the authors should illustrate the number of baseline data collectors. Given that there is a risk of human data collection error assigning data checks to more than one researcher should be necessary.
	8. A statement that physiotherapists have equal qualifications should ensure identical intervention.
	9. The protocol does not explain if the procedure of allocating each participant to a physiotherapist is randomized in the section "Randomisation and Blinding".

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
Introduction: The authors can consider to add why balance is impaired in people with MCI, and why addressing balance impairment can reduce falls in this population. There are many risk factors contributing to falls in people with MCI, so providing more information about the association between MCI, balance and falls can strengthen the rationale of the study.	Reasons have been included as to why people living with MCI have impaired balance and more information has been included about the association between MCI, balance and increased risk of falls (see page 5, lines 12-15). Also included further down in the Introduction we have addressed how balance exercises may reduce falls in this population (page 5, lines 25-27 the following paragraph).
Page 6 Line 34: Why did you choose 4-square step test as the balance measure, and use 3 different measures for physical performance?	The 4-square step test was used as the primary outcome measure for balance for this project because it specifically measures dynamic standing balance. It also requires the person with MCI to use their cognition to complete the test (i.e. completing the step pattern correctly) and to step forwards, sideways and backwards which can be challenging. It also has excellent test-retest reliability (ICC = 0.98). Different balance outcomes (predominantly not primary outcomes) have been used across the 8 RCTs described in the Introduction section of the protocol. However, none used a specific balance test, they usually combined dynamic balance and functional mobility by using the TUG, Tinetti Performance Oriented Mobility Assessment and the Short Physical Performance Battery (SPPB). Three different measures were used for physical performance because it is known that falls risk for people living with MCI includes gait parameters (see Introduction section) which the SPPB includes, TUG is a measure of functional mobility and is used widely in research with older adults and those with cognitive impairment. The TUG was also included for comparison with other studies reporting outcomes with this population, with added potential for future pooling of our results with other studies. The 6-MWT was included to determine if the walking program had improved endurance and aerobic capacity of the participants, given the strong evidence that aerobic exercise benefits brain health and function.
Methods and analysis: According to the guideline of BMJ Open, the date of the study should be included in the	The date of the study has been included, see page 7, lines 12-13.

methods.	
Participants: Page 7 Line 24: Do you have a specific timeframe of not participating in any balance training before joining the exercise intervention?	There was no specific timeframe regarding not participating in balance training before the exercise intervention. As noted in the inclusion criteria if the participant was not meeting the Australian physical activity guidelines (<150minutes of "moderate intensity" physical activity a week self-reported) and not participating in balance training regularly (< twice a week) they could be considered for the study (i.e. need to meet all other inclusion criteria also). The reason no time period was given for participating in balance training was because, say for example someone had participated in balance training five years prior, de-training would have occurred during this time. However, if they were completing one balance training session a week and not meeting the other physical activity guidelines they would be eligible for participation. This is because our expectation is to be participating in 120 minutes of balance training per week and one session is unlikely to be achieving this. To date very few people who we have screened are participating in any type of balance exercises currently (or ever).
Outcomes and assessments: Page 10 Line 25: Do you have any measures to accommodate the memory deficits of the participants (e.g., they may forget to jot down the falls information in the falls calendar and they are unable to recall afterwards)?	At each monthly call the Research Officer will ask each participant about their calendar, if they are having any difficulties completing it and to place it somewhere they can see it regularly as a reminder to complete it should a fall occur. We will also ask them if they have had any falls that were not recorded in the calendar as well. This has been added to the text, see page 10, lines 13-15
Page 11 Line 39: the use of FES-I was not mentioned in the study objectives and hypothesis. This should be added.	FES-I has now be included in the study objectives and hypothesis, see page 6, lines 22, 28-29.
Intervention: Page 13 Line 28: Can you explain why a walking component has been included in the exercise intervention? What is the additional use of walking exercise if the aim of this study is to evaluate the effects of a balance exercise program?	A walking component has been included in the intervention because the evidence is strong that aerobic activity is good for cognitive health and function for people living with MCI. This has now been included in the Introduction see page 5-6, lines 35, 1-4. Due to this reason, it seemed unethical not to include an aerobic component to the intervention.
Page 13 Line 38: Apart from prescribing the exercise intervention, do you have any strategy to increase the physical activity of the participants? I'm asking because "motivational" phone calls will be made during the course of the intervention but the investigators did not mentioned what will be done in the phone calls.	Additional information has been included on page 13-14, lines 35-36, 1-2 about the "motivational" phone calls and working with each participant to increase their participation in the intervention.
Reviewer 2	
1. The authors identified prevalences of MCI in different areas. It would also be valuable to give a comprehensive description of the ponderance about MCI. However, some data is outdated. I conducted a brief literature search and	The literature has been updated for prevalence of MCI in various countries, see page 5, lines 3-4.

identified a few recently published works (you might find more): Jia, L., Du, Y., Chu, L., Zhang, Z., Li, F., Lyu, D., . . . Group, C. (2020). 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, 5(12), e661-e671. doi:10.1016/S2468-2667(20)30185-7	
2. The text could use a comprehensive revision for literary expression.	The text has been checked and updated with the most recent literature. Please note Endnote references do not show as track changes but if required can be highlighted for the reviewer.
3. It is unclear that how the study adjusts confounding factors. Considering the complexity of falling, I would not recommend it as the primary outcome.	With our large sample size (n=396) randomisation should remove the need for adjustment for confounding variables. As described in the protocol (statistical analysis section) the only planned adjustment is for participant's observation time. However, if there are any significant differences between demographic factors that may have a confounding effect then these will be included in models as covariates. Falls are the critical outcome of interest for this study, given the high falls rates in people with MCI. While other measures such as balance performance are useful surrogates, and provide information to inform mechanisms underlying any positive outcomes identified, changes on these measures do not always translate into a reduction in falls. Our team have extensive experience in falls prevention trials in older people with multiple co-morbidities, including those with more severe cognitive impairments than MCI (eg Alzheimer's disease), and have successfully implemented approaches to obtain accurate falls data. For these reasons we consider falls should remain our primary outcome.
4. The protocol uses two kinds of cognition assessment measurements: Standardised Mini-Mental State Examination (SMMSE) in the screening process and Montreal Cognitive Assessment (MOCA) Test in the outcome assessment process. Please explain the reason for the inconsistency.	The Petersen criteria were used to determine diagnosis of MCI (see page 7 Participants section). The SMMSE and the Cognitive Dementia Rating (CDR) have been used as measures to classify participants as MCI in numerous research studies and as such was used again here. The MOCA is a more commonly used cognitive tool by allied health practitioners in Australia (potentially other countries as well) and as such, it is being used as a secondary outcome measure in this study. This will allow for interpretation by healthcare practitioners and translation of the intervention should the results illustrate significant changes to efficacy and effectiveness.
5. The protocol does not make a strategy to reduce withdrawal. I recommend you offer the allowance to participants at each intervention stage, or you can take other ways to enhance the adherence.	The funding for this study does not allow for participants to be remunerated for their participation, however our previous experience in other falls prevention trials with various groups of older people with multiple co-morbidities, have shown the monthly calls (to collect falls data) are valued by participants, and help keep the participants interested. The intervention participants also have phone calls with their physiotherapists as well as the home visits which we believe will assist with adherence also. Withdrawal rates were included in the sample size calculations at 20% for the initial 6-month intervention period and then another 15% for the following 6-months.
6. In the "Outcomes and Assessments" section, the	The secondary outcomes are described across two pages (p10-11) and unfortunately due to word limits it is not possible to

authors had better summarize the secondary outcomes.	include further detail. A more thorough description could be included as a supplementary on-line document if requested by the reviewer. These tools are commonly used by researchers around the world within this area and it was determined that the detail and referencing provided would be adequate for researchers to be able to replicate the study.
7. In "Randomisation and Blinding", the authors should illustrate the number of baseline data collectors. Given that there is a risk of human data collection error assigning data checks to more than one researcher should be necessary.	The number of data collectors has been included (i.e. three), see page 12, line 7-8. An additional comment has been included in the Data Monitoring section describing data entry checking also, to minimise the risk of error (page 17, lines 13-14).
8. A statement that physiotherapists have equal qualifications should ensure identical intervention.	A statement has been added that all staff delivering the intervention will be qualified physiotherapists, with a background in working with older adults and people living with cognitive impairment. They will have also undertaken training prior to delivering the intervention, see page 12, lines 29-31.
9. The protocol does not explain if the procedure of allocating each participant to a physiotherapist is randomized in the section "Randomisation and Blinding".	Please see the highlighted section in the "Randomisation and Blinding section" as well as additional text that has been added to clarify that randomisation occurs by the lead researcher pressing the randomisation button on the REDCap system. If a participant is in the intervention group an email with their details is automatically generated by the REDCap system and is sent to the lead researcher who then allocates that intervention participant to one of the intervention physiotherapists, based on their availability. Page 12, lines 7-11.

VERSION 2 – REVIEW

REVIEWER	Chan, Wayne The Hong Kong Polytechnic University, Rehabilitation Sciences
REVIEW RETURNED	01-Feb-2022

GENERAL COMMENTS	The authors have generally addressed the concerns suggested by the reviewers. Given the fact that the study is ongoing, the authors , however, should be aware that some concerns about the methodology may still exist, and the authors may encounter similar comments when the report of the study is submitted for publication.