PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of a home-based Radio-Taiso exercise programme on health-related quality of life in older adults with frailty: protocol for an assessor-blind randomised controlled trial
AUTHORS	Osuka, Yosuke; Kojima, Narumi; Sugie, Masamitsu; Omura, Takuya; Motokawa, Keiko; Ueda, Takuya; Maruo, Kazushi; Ono, Risa; Aoyama, Toshihiko; Inoue, Shigeru; Kim, Hunkyung; Sasai, Hiroyuki

VERSION 1 – REVIEW

REVIEWER	Jack Dalla Via School of Exercise and Nutrition Sciences
REVIEW RETURNED	22-Jun-2022

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. It is a detailed, well-written protocol for an interesting study investigating a pragmatic and scalable exercise intervention, which includes a comprehensive set of outcome measures. Below are some specific comments for consideration. Abstract: 1. The word 'attend' in the sentence "The primary aims of this trial is to test whether older adults with frailty who attend our home-based…" is confusing as the exercise was home-based. I suggest changing it to something along the lines of 'who complete our' or 'who are prescribed our'. 2. I suggest the tool used to assess HR-QoL be included in the abstract, especially as it is the primary outcome. Introduction: 3. Grammatical error in the second sentence. It starts with "A research showed that", which doesn't read clearly. 4. There are some contradictory statements in the second paragraph. Initially you say that interventions in frailty have exclusively focused on physical outcomes, then later say that exercise are the most effective in improving HR-QoL in those with frailty. Perhaps change the word 'exclusively' to something less definitive (e.g. predominantly or mostly). Methods and analysis: 5. The duration of the study should be included in the sentence describing the study design. E.g. 'A 12-week randomised…' 6. The paragraph on ethics can be removed from the 'Study design, setting, procedure, and ethics' section of the methods. This information on ethics should instead be incorporated into the 'Ethics and Dissemination' section before the discussion. 7. The authors state that outcome assessments will be conducted in June and September, but it should be made clearer that it is a 12-

	week follow-up. A simple sentence under the 'Outcome measures' or 'Assessments' subheading, stating that all outcomes will be assessed at baseline and at 12-week follow-up would suffice. 8. I suggest the authors specify how exclusion criteria 3 will be assessed. 9. Can the authors include information about the recruitment rate from the previous pilot trial? This would help to show that the plan to recruit 226 participants in 1 month is feasible. 10. Towards the bottom of page 7 in the paragraph about the pilot study results, the authors state that there were no improvements in physical outcomes. What specific physical outcomes were assessed? I cannot imagine that simply increasing the number of supervised sessions will lead to significantly greater physical outcomes, especially considering adherence was extremely high. Looking at the supplementary tables, the exercise program does not appear to involve many, if any, resistance or aerobic type exercises so I would argue that the lack of physical improvements is more likely due to the nature of the exercise program (predominantly flexibility and balance). 11. Under the 'Assessments' subheading, the word 'some' is confusing. Does this mean that only certain outcomes are objective, or only certain outcomes are blinded? Consider rewording this sentence to clarify. 12. Under the 'Frailty phenotype' subheading, a reference is needed for Fried's frailty criteria. 13. Usual gait speed and hand grip strength appear to only be performed once. Grip strength in particular is typically performed 3 times with the highest value used in the analysis. 14. For habitual physical activity and sleep accelerometry, please specify the 7-day windows of time that will be used at baseline and follow-up in relation to collection of the other study outcomes and the intervention starting/finishing. 15. For the statistical analysis, the authors state that an intention-to-treat analysis will be performed and that all participants will be analysed irrespective of whether they comply with the study protocol. But then state that those who didn't participate in the intervention or who do not have follow-up data will be excluded. This seems contradictory and requires clarification.

VERSION 1 – AUTHOR RESPONSE

Responses to comments made by Dr. Jack Dalla Via (Reviewer #1)

Major comments

Thank you for the opportunity to review this manuscript. It is a detailed, well-written protocol for an interesting study investigating a pragmatic and scalable exercise intervention, which includes a comprehensive set of outcome measures. Below are some specific comments for consideration.

Response: Thank you very much for your careful review of our manuscript. All comments were constructive and have promoted readability of our manuscript.

Abstract:

1. The word 'attend' in the sentence "The primary aims of this trial is to test whether older adults with frailty who attend our home-based…" is confusing as the exercise was home-based. I suggest changing it to something along the lines of 'who complete our' or 'who are prescribed our'.

Response: We have revised this as below.

*"The primary aims of this trial is to test whether older adults with frailty who are prescribed our home-based Radio-Taiso exercise programme will receive greater benefits for HR-QoL compared to those who are not prescribed the exercise programme." (**Page 2, lines 7–10**).*

2. I suggest the tool used to assess HR-QoL be included in the abstract, especially as it is the primary outcome.

Response: We have added an explanation that HR-QoL will be assessed using the SF-36®, as stated below.

*"The primary outcome is the change in the mental domain of HR-QoL assessed using SF-36®." (**Page 2, lines 20–21**).*

Introduction

3. Grammatical error in the second sentence. It starts with "A research showed that", which doesn't read clearly.

Response: We have revised this sentence as below.

*"Research suggests that 7% and 47% of older adults have frailty and pre-frailty, respectively, and their risk of falls, disabilities, nursing home admission, and death is significantly higher than that of robust older adults.[1]" (**Page 4, lines 3–6**).*

4. There are some contradictory statements in the second paragraph. Initially you say that interventions in frailty have exclusively focused on physical outcomes, then later say that exercise are the most effective in improving HR-QoL in those with frailty. Perhaps change the word 'exclusively' to something less definitive (e.g. predominantly or mostly).

Response: We have revised this sentence as below.

*"Interventions such as exercise and nutritional programmes are useful for reducing the prevalence of frailty, but stakeholders have raised concerns that research on these interventions has focused predominantly on improving physical outcomes.[2]" (**Page 4, lines 10–12**).*

Methods and analysis

5. The duration of the study should be included in the sentence describing the study design. E.g. 'A 12-week randomised…'

Response: We have revised this sentence as below.

*"This is a 12-week randomised, assessor-blind, parallel-design, two-arm, phase III trial." (**Page 5, lines 7–8**).*

6. The paragraph on ethics can be removed from the 'Study design, setting, procedure, and ethics' section of the methods. This information on ethics should instead be incorporated into the 'Ethics and Dissemination' section before the discussion.

Response: We have moved this paragraph to the "Ethics and Dissemination" section.

"ETHICS AND DISSEMINATION

The research protocol will be conducted in accordance with the Declaration of Helsinki. The Research Ethics Committee of TMIG approved the protocol on 16 December 2021. The study protocol was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) on 20 March 2022 (trial registration no. UMIN000047229). All amendments to the study protocol will be disclosed to UMIN-CTR.

*Study results will be presented at international scientific conferences and reported in peer-reviewed international journals. After publication, a summary of the results will be published on the TMIG and Japan Post Insurance Co., Ltd., websites." (**Page 16, lines 22–31**).*

7. The authors state that outcome assessments will be conducted in June and September, but it should be made clearer that it is a 12-week follow-up. A simple sentence under the 'Outcome measures' or 'Assessments' subheading, stating that all outcomes will be assessed at baseline and at 12-week follow-up would suffice.

Response: We have added the sentence below to the "Outcome" section.

*"All outcomes excluding habitual physical activity will be assessed at a baseline survey within 2 weeks prior to the start of the intervention and at a follow-up survey within 1 week after the end of the intervention (Figure 3)." (**Page 8, lines 25–28**).*

8. I suggest the authors specify how exclusion criteria 3 will be assessed.

Response: The exclusion criteria 3 will be assessed by self-reports. We have added an explanation regarding the method of assessing exclusion criteria 3, as below.

*"3) self-reports of being unable to eat, excrete, dress, move, or bathe independently." (**Page 5, lines 26–27**).*

9. Can the authors include information about the recruitment rate from the previous pilot trial? This would help to show that the plan to recruit 226 participants in 1 month is feasible.

Response: We have added information about the recruitment rate of our pilot trial as below:

*"Of these, 514 (60%) met the pre-frailty or frailty criteria and 186 (recruitment rate: 20.6%) met all eligibility criteria and were willing to participate." (**Page 6, lines 3–5**).*

10. Towards the bottom of page 7 in the paragraph about the pilot study results, the authors state that there were no improvements in physical outcomes. What specific physical outcomes were assessed? I cannot imagine that simply increasing the number of supervised sessions will lead to significantly greater physical outcomes, especially considering adherence was extremely high. Looking at the supplementary tables, the exercise program does not appear to involve many, if any, resistance or aerobic type exercises so I would argue that the lack of physical improvements is more likely due to the nature of the exercise program (predominantly flexibility and balance).

Response: We mostly agree with the reviewer's comment. In the pilot study, mobility was primarily assessed using the Short Physical Performance Battery. As the reviewer has highlighted, Radio-Taiso may not include properties that improve mobility. Although Radio-Taiso predominantly consists of flexibility exercises, a thorough completion of the purpose of each movement in Radio-Taiso necessitates quicker and larger movements, which require muscle endurance and whole-body endurance. Although the face-to-face instructions in the pilot study were reduced from three to one due to the fourth wave of COVID-19, several participants who attended the face-to-face instruction session commented, "The quality of practice is different between just imitating the moves on TV or

DVD and understanding the purpose of the movements through face-to-face instruction. I think face-to-face instruction should be increased". Thus, we decided to increase face-to-face instructions to improve the quality of the movements of Radio-Taiso in this trial. Additionally, we decided to add endurance (2-minute step-in-place test), muscular endurance (chair stand test), and upper body flexibility (back scratch test) outcomes, which may be improved by practicing Radio-Taiso, and to assess them exploratively as secondary outcomes. We have added this explanation as below.

> *"Radio-Taiso may not include properties that significantly improve physical outcomes because it predominately consists of flexibility exercises. However, thoroughly completing the purpose of each movement in Radio-Taiso necessitates quicker and larger movements, which require muscle endurance and whole-body endurance. In this regard, several participants who received face-to-face instructions in the pilot study reported that it is important to understand the purpose of each movement of the Radio-Taiso via face-to-face instructions to improve the quality of practice at home. Thus, to provide participants with a programme that yields better physical outcomes, the number of face-to-face sessions will be increased from three to six and include processes that help participants familiarise with the key points of the programme." (**Page 7, lines 27–36**).*

11. Under the 'Assessments' subheading, the word 'some' is confusing. Does this mean that only certain outcomes are objective, or only certain outcomes are blinded? Consider rewording this sentence to clarify.

Response: To clear the confusion, we have revised the sentence as below:

> *"Objective outcomes including physical fitness, posture, cognition, BDNF, and physical activity will be assessed by research staff blinded to allocation information." (**Page 8, lines 36 to page 9 line 1**).*

12. Under the 'Frailty phenotype' subheading, a reference is needed for Fried's frailty criteria.

Response: We have added a relevant reference for Fried's frailty criteria.

> *"Frailty phenotype will be assessed using Fried's frailty criteria, characterised by five limitations: slowness, weakness, exhaustion, low activity, and weight loss.[1]" (**Page 9, lines 14–15**).*

13. Usual gait speed and hand grip strength appear to only be performed once. Grip strength in particular is typically performed 3 times with the highest value used in the analysis.

Response: Unfortunately, we were unable to repeat these assessments, as we had to minimise survey time on trial-ready cohorts in 2020 due to a fifth wave of COVID-19. However, the impact of measurement error is considered as negligible, since the assessments are ultimately used as binary variables.

14. For habitual physical activity and sleep accelerometry, please specify the 7-day windows of time that will be used at baseline and follow-up in relation to collection of the other study outcomes and the intervention starting/finishing.

Response: We have added information regarding the 7-day time window as below:

> *"Participants will be instructed to wear the device around the waist for 7 days from baseline and follow-up assessments during all activities of daily living from waking to bedtime, except for underwater activities (e.g. bathing and swimming)." (**Page 14, lines 5–7**).*

15. For the statistical analysis, the authors state that an intention-to-treat analysis will be performed and that all participants will be analyzed irrespective of whether they comply with the study protocol. But then state that those who didn't participate in the intervention or who do not have follow-up data will be excluded. This seems contradictory and requires clarification.

Response: The term ITT may be confusing because different researchers use different definitions. We will use a full analysis set (FAS) for the primary analysis, based on the guidelines of the International Council for Harmonisation.[3] Although the ITT principle includes all randomised participants, it is almost impossible to thoroughly follow-up participants in real-world clinical trials. Therefore, many clinical trials apply the FAS to the main analysis as closely as possible to the ideal approach of ITT. The FAS approach is generally recommended as a conservative strategy. Excluded cases from the FAS are limited. These include cases that 1) violated the eligibility criteria, 2) have never been treated, and 3) lacked follow-up data. We have revised the relevant paragraph as below:

> *"The results of the main analyses will be interpreted based on the intention-to-treat principle. The full analysis set will exclude participants who 1) are subsequently identified to not meet the eligibility criteria; 2) never participated in the intervention programme; or 3) lack post-randomisation data[3] and will be applied as the main analysis population. The International Council for Harmonisation guidelines recommend applying a full analysis set that excludes these participants from the main analyses as a conservative strategy.[3]" (**Page 15, lines 29–35**).*

VERSION 2 – REVIEW

REVIEWER	Jack Dalla Via School of Exercise and Nutrition Sciences
REVIEW RETURNED	25-Aug-2022

GENERAL COMMENTS	Thank you to the authors for thoroughly responding to my comments. I am satisfied that all comments have now been approproately addressed.