PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Effectiveness of the ARTHE-e app for exercise adherence in people with knee osteoarthritis: protocol for a randomized controlled trial

Authors

Pelletier-Visa, Mathilde; DOBIJA, Lech; BONHOMME , Alexis; Lanhers, Charlotte; Pereira, Bruno; Coudeyre, Emmanuel

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Liang, Shuang**
Affiliation	**The University of Sydney**
Date	**13-Aug-2024**
COI	**None**

1. The 'Strengths and limitations of this study' are not clearly stated as currently primarily describe the methods, please revise.

2. The rationale presented in lines 113-117 could be enhanced. There have been 12 RCTs published on this topic, while adherence was not their main outcome, did any of these studies report on adherence? What's the size and quality of these RCTs?

3. Lines 161-162 state that a total of 144 participants will be recruited, while the target is 120. Good to include a statement to clarify the reasoning e.g., account for potential loss to follow-up or withdrawals.

4. Randomisation: "the list is generated before the trial and saved centrally", could we please further clarify as to how randomisation concealment will be ensured.

5. Procedures and schedule: would be good to provide a more comprehensive and cohesive description as it currently consists of isolated sentences/phrases.

6. Table 2: Other outcomes, timepoints for Application use was not specified in the table. If this is extracted on a monthly basis perhaps state this within the study period (post randomisation)

7. Please specify how the questionnaires will be administered – e.g., electronically? This pertains to the section starting from line 202.

8. The abstract states that the primary outcome being the between-group difference in EARS score at 6 months, whereas the methods section indicates multiple timepoints (2, 4, and 6 months).

9. Management of the study – this section appears to duplicate some content from the method section. Could this be weaved into the method section, and develop this section to detail aspects such as data management and project management plans.

10. Typo in line 133, should read: "The assessor conducting the final study evaluation will BE blinded."

11. Suggest replacing some of the older references with more recent literature.

Reviewer **2**

Name **Zeiler, Michael**

Affiliation **Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute for Medical Informatics, Biometrics and Epidemiology**

Date **16-Aug-2024**

COI **none**

- Line 146: Please refer to the case number planning (Line 342ff.), as the number of 120 study participants seems rather random at this point.

- Table 1: Inclusion Criteria: Please specify why the study participants must be between 40 and 85 years old.

Please add a description of who (which professional group) will carry out what during the study? I think it would also be useful to add the information about who carries out which assessment to Table 2.

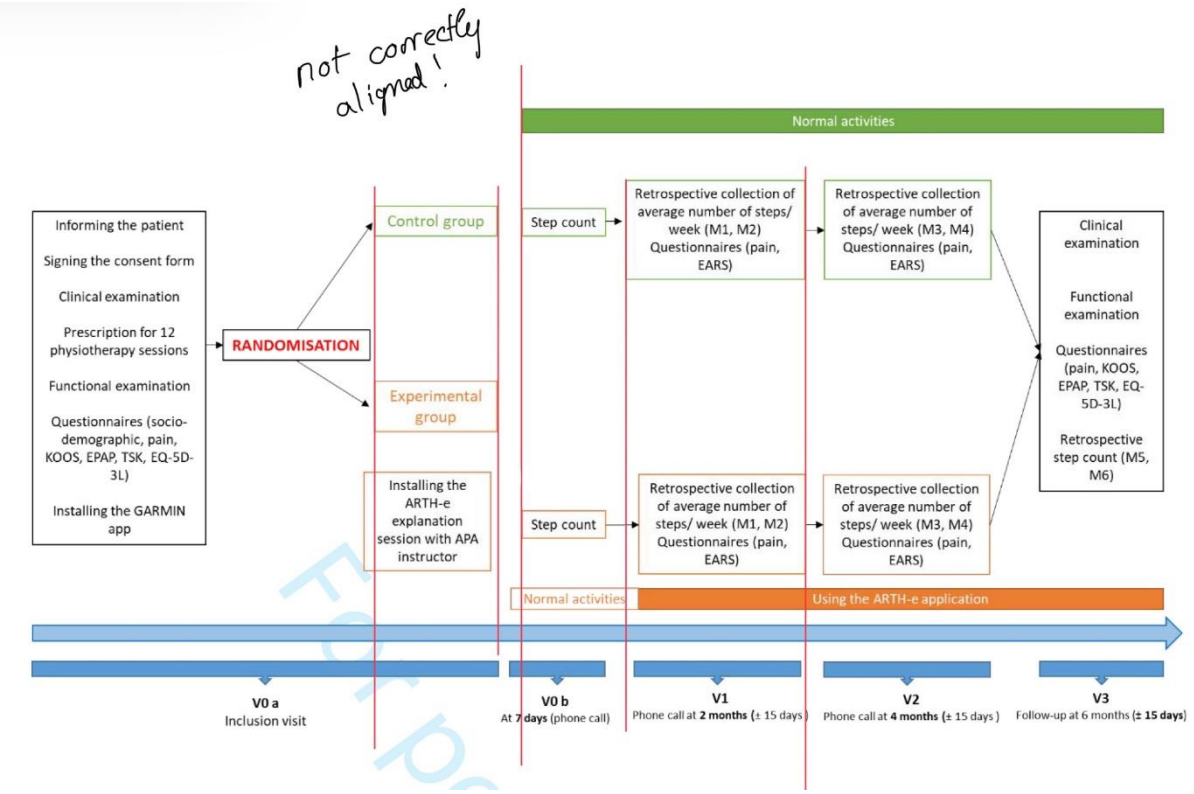
- Line 152: Please describe in this paragraph which professional group is covered by the term 'investigator'. Is this the medical or nursing staff or physiotherapists?

- Line 172: Same mentioned thing with "second assessor"

- Line 203: Who is the "investigator"? Is it the same person who carried out the study clarification?

- Line 426: Who is this blinded second assessor?

- Line 222: Figure 2: This graphic shows the course of the patients' studies very well! However, in the version I have, the boxes are not aligned (see attached screenshot). I recommend checking the chart again and adjusting the size and position of the boxes.



Reporting Step-Count: Please clarify

- Line 233: Do you have access to the actual data from the wristband, or do you have to rely on the study participants' report over the phone?

- Line 308: Is only the number of steps taken in the past week before the phone call or is an overall average of the steps taken in the past weeks used?

- Line 265: Please add how are technical problems with the app dealt with during the intervention? Are these recorded to further improve the usability of the app?

- Line 396: unpaired t-test

- Line 430ff.: Is there a publication on the results of the predecessor / pilot study?

Reviewer	**3**
Name	**Weddell, Joseph**
Affiliation	**The University of Sydney, Sydney Nursing School**

Date 28-Aug-2024

COI None to disclose

Thank you for the opportunity to review the protocol for this important and interesting trial. The manuscript is well written, comprehensive and clearly thought out. I have some minor feedback to give you that you may wish to consider:

Page 6, line 133 - the word "be" is missing after "will" and before "blinded"

Page 7, exclusion criteria - I am just wondering what is the rationale behind excluding pregnant women in this study? It may be worth briefly clarifying.

Page 8, line 204 - are you also collecting marital/partner status in the sociodemographic data? Being married or partnered has been associated with higher adherence to exercise prescriptions/programs in other conditions and it may be worth considering the impact of this in your manuscript.

Page 10, line 269 - you note that the control group will receive a booklet with a series of exercises designed to relieve pain, and then state that randomisation to the control group "will not change the daily life and activities of the participants." As you cannot definitively say that the care received in the control group (i.e. booklet) will or will not impact some change to daily life or activities, I would suggest rewording to something along the lines of "the control group will receive standard care, which in France consists of a booklet that..." etc

Page 12, line 287 and page 15, line 444 - "barriers and levers", by which you mean barriers and facilitators (as noted in the same section) - is the word "lever" commonly used for "facilitators"? I have not come across the word "lever" used in this context before, and I would change it for facilitators unless it is the official name for this tool.

Page 15, line 444 - the secondary outcomes of this study are worded a little unclearly in this passage, i.e. "thanks to pain levels", "barriers and leavers" and "the medici-economic section". Please could you reword to clearly state the secondary outcome variables.

Pages 11,12 and 15 - for the included tools - have these tools been validated in studies with osteoarthritis populations? If so, please note this and provide citation(s).

Thank you for the opportunity to review this well written protocol, and good luck with the trial.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. Shuang Liang, The University of Sydney, University of New South Wales Medicine & Health

Comments to the Author:
1. The 'Strengths and limitations of this study' are not clearly stated as currently primarily describe the methods, please revise.
Thank you for your comment, Limitation have been added to this section.
Line 65to 77 :

- ➔ "We will test a new application developed by healthcare professionals that integrates user feedback and current recommendations.
- ➔ Intervention addressed only to patients motivated to perform exercises.
- ➔ Effects analyzed only up to 6 months, with no long terms effects
  The impact of using the application on many aspects of knee osteoarthritis will be evaluated, from the body structures and functions level to quality of life.
- ➔ Adherence to exercises measured in a declarative manner (questionnaire), however step count and connection to application will indirectly measure physical activity and use of the application which are complementary to the construct of adherence to exercises."

2. The rationale presented in lines 113-117 could be enhanced. There have been 12 RCTs published on this topic, while adherence was not their main outcome, did any of these studies report on adherence? What's the size and quality of these RCTs?
Thank you for your comment. We researched these studies again and specified the information requested.
Line 115-120 : "Despite the widespread use of m-health applications, to our knowledge, only 11 randomized controlled studies have been published worldwide on their efficacy in terms of non-pharmacological management. These studies used several criteria to assess exercise adherence, including the EARS questionnaire, number of steps with a connected bracelet, analysis of app extracts and self-reported adherence. The authors included an average of 208 patients. Of the 11 studies selected, only 1 used the EARS questionnaire as the primary endpoint."

3. Lines 161-162 state that a total of 144 participants will be recruited, while the target is 120. Good to include a statement to clarify the reasoning e.g., account for potential loss to follow-up or withdrawals.
Thank you for this comment. Our goal is to recruit 120 patients. The calculation of the number of people lost to follow-up is taken into account in the "Statistical analysis" section and therefore in the number of subjects necessary. We decided to include an additional 18 patients, i.e. 120 instead of 102, in order to anticipate patients lost to follow-up. A correction has been made in this regard.
Line 177-179: "To ensure the inclusion of the 120 planned participants, each participating center should include 2 patients minimum per month for 18 months taking into account those lost to follow-up."

4. Randomisation: "the list is generated before the trial and saved centrally", could we please further clarify as to how randomisation concealment will be ensured.
Thank you for your comment. This is an error. The randomization was performed by minimization on Ennov using an algorithm. The sentence has been deleted from line 184.

5. Procedures and schedule: would be good to provide a more comprehensive and cohesive description as it currently consists of isolated sentences/phrases.
We have taken your comment into account and have made some changes from line 194: "The evaluations carried out at each visit are described in table II. APA instructors, physiotherapists and doctors have been trained to study and carry out the various assessments

for the management of patients with a knee osteoarthritis."

6. Table 2: Other outcomes, timepoints for Application use was not specified in the table. If this is extracted on a monthly basis perhaps state this within the study period (post randomisation)

Thank you for this pertinent remark. Indeed, we have added this information in table II (page 8). The extraction of usage data is carried out every month after randomization of the patient.

7. Please specify how the questionnaires will be administered – e.g., electronically? This pertains to the section starting from line 202.

Thank you for this comment. Indeed, we specified in the text, line 211 and 214 that the questionnaires were completed on site in paper version.

Line 211 : "Then, they will collect sociodemographic (age, sex, weight, height, education status and socio-professional category) and medical data (history of knee osteoarthritis pain and treatments) delivered to the patient in paper form during the on-site visit."

Line 214 : "The investigator (medical team) will rate the Kellgren and Lawrence classification for assessing osteoarthritis severity, evaluate knee flexion and extension using a goniometer, and the patient complete the questionnaires in paper form"

8. The abstract states that the primary outcome being the between-group difference in EARS score at 6 months, whereas the methods section indicates multiple time points (2, 4, and 6 months).

As part of this research protocol, we want to evaluate the evolution of the EARS questionnaire score and therefore measure a delta between 2 and 6 months.

We have made a correctionin the abstract line 52 : "The primary outcome will be the difference betweengroups in the evolution of the EARS score at 6 months."

9. Management of the study – this section appears to duplicate some content from the method section. Could this be weaved into the method section, and develop this section to detail aspects such as data management and project management plans.

This section was deleted and implemented in the method part. Redundancies have been avoided in line 171 and 252.

10. Typo in line 133, should read: "The assessor conducting the final study evaluation will BE blinded."

Thank you for your correction. The correction has been made.

Line 142 : The assessor conducting the final study evaluation will be blinded to the participants' group allocation."

11. Suggest replacing some of the older references with more recent literature.

Thank you for your comment.

Various bibliographies have been updated: 3(line 550), 4 (line 553), 16 (line 588), 24 (line 615), 26 (line 622)

Line 550 : "Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578-1589. doi:10.1016/j.joca.2019.06.011 »

Line 553 : Moseng T, Vliet Vlieland TPM, Battista S, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis: 2023 update. *Ann Rheum Dis*. Published online January 11, 2024:ard-2023-225041. doi:10.1136/ard-2023-225041

Line 588 : Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, CONSORT NPT Group. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med*. 2017;167(1):40-47. doi:10.7326/M17-0046
Line 615 : G B, G B. [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. *Monaldi Arch Chest Dis Arch Monaldi Mal Torace*. 2012;78(3). doi:10.4081/monaldi.2012.121
Line 622 : "Almeida GPL, Monteiro IO, Dantas RG de O, Tavares MLA, Lima PO de P. Reliability, validity and responsiveness of the Step Up and Down (StUD) test for individuals with symptomatic knee osteoarthritis. *Musculoskelet Sci Pract*. 2021;56:102454. doi:10.1016/j.msksp.2021.102454 »

Reviewer: 2
Mr. Michael Zeiler, Friedrich-Alexander-Universität Erlangen-Nürnberg

Comments to the Author:
• Line 146: Please refer to the case number planning (Line 342ff.), as the number of 120 study participants seems rather random at this point.
Thank you for this remark. We have specified this point line 155, "We will recruit based on our sample size estimation described in below statistical analyses section, 120 participants aged between 40 and 85 years with symptomatic knee osteoarthritis (according to EULAR)".

• Table 1: Inclusion Criteria: Please specify why the study participants must be between 40 and 85 years old.
Thank you for your comment. We chose the age range 40 to 85 years for the recruitment of participants in our study because of the well-established clinical and epidemiological features of knee osteoarthritis, and to ensure adequate representation of the different phases of evolution of this pathology. Onset of knee osteoarthritis before the age of 40-50 is relatively rare, and is often classified as early osteoarthritis. In these cases, knee osteoarthritis is generally secondary to specific factors, such as joint trauma (e.g. ligament or meniscus injuries), intensive sport or structural abnormalities of the knee (genu varum or valgum).
Our choice to start recruitment from the age of 40 takes into account the need to include these early cases while minimizing the potential bias that could arise from including younger participants, in whom osteoarthritis is much less common and often due to specific conditions not representative of the general population.
The prevalence of knee osteoarthritis increases sharply with age, with a peak observed in individuals aged between 60 and 70. In this age bracket, knee osteoarthritis is generally idiopathic, linked to the natural aging of articular cartilage, and reaches a high frequency in the general population. This period therefore represents a critical phase for observing the natural progression of the disease and its associated factors. The inclusion of this age group enables us to capture the most common clinical features of knee osteoarthritis, as well as measure the functional impact on quality of life in this population, which is often the most affected. We chose to limit our recruitment to 85-year-olds, because beyond this age, individuals' knees are often characterized by severe cartilage degeneration due to advanced aging. This degeneration, coupled with other comorbidities common in the elderly (such as osteoporosis or mobility disorders), can make it difficult to attribute symptoms specifically to knee osteoarthritis alone.
Line 157-160 : "We chose the age range of 40 to 85 years to include early cases of knee osteoarthritis (OA) that often arise from trauma or structural abnormalities before 50, while

capturing the peak prevalence of idiopathic OA between 60 and 70 years. Beyond 85, severe cartilage degeneration and comorbidities complicate symptom attribution solely to OA."

Please add a description of who (which professional group) will carry out what during the study? I think it would also be useful to add the information about who carries out which assessment to Table 2.
In accordance with your recommendation, we have detailed the health professionals involved in the various assessments. To do this, we have used * to differentiate between the different professionals.
Table II : "*Performed by the physician, **performed by a Clinical research Associate, *** performed by adapted physical activity (APA) instructor, **** performed by the patient alone"

• Line 152: Please describe in this paragraph which professional group is covered by the term 'investigator'. Is this the medical or nursing staff or physiotherapists?

Thank you for your comment. It wasn't clear. We have clarified this point. Investigators are part of the medical team, a physician.
Line 175:" Potentially eligible individuals will be informed about the study during a consultation with one of the investigators (physician)."

• Line 170: Same mentioned thing with "second assessor"

We have also clarified this point, it's a physician other than the first investigator in line 189 : Group allocation will be blinded to the second assessor (a physician investigator from the medical team) who will carry out the final study visit."

• Line 203: Who is the "investigator"? Is it the same person who carried out the study clarification?
The investigator is a physician from the Physical and Rehabilitation Medicine department who is responsible for the patient's inclusion. A second physician will see the patient at 6 months and will be blinded to the group allocated to the patient so as not to bias the medical examination.
Line 214: "The investigator (medical team) will rate the Kellgren and Lawrence classification …"

• Line 426: Who is this blinded second assessor?
Thank you for this comment. I have clarified this point.
Line 189-190: "a physician investigator from the medical team"

• Line 222: Figure 2: This graphic shows the course of the patients' studies very well! However, in the version I have, the boxes are not aligned (see attached screenshot). I recommend checking the chart again and adjusting the size and position of the boxes.
Thank you for your comment, the figure has been revised with the corrections requested and implemented in the 'figure' document in an editable version. Also, the study schedule was revised in a modifiable version.

Reporting Step-Count: Please clarify
• Line 233: Do you have access to the actual data from the wristband, or do you have to rely on the study participants' report over the phone?

We have no right of access to the GARMIN connect application on the wristband. We have to rely on what is recorded on their monthly report. We have added a correction according to your comment to this effect on line 240 : " The patient will record their average daily step count and report it to the CRA, as the CRA will not have access to the GARMIN application."

• Line 308: Is only the number of steps taken in the past week before the phone call or is an overall average of the steps taken in the past weeks used?
Initially we decided to base the number of steps on the previous week only. This is too complicated for patients to set up, as they have to keep an eye on the dates in order to put the watch on at the right time. To correct this, we told them to wear the watch from the moment they woke up until the moment they went to bed for the duration of the study. But as you said, we are basing ourselves on the average number of steps per month retrospectively for all the patients in the study. The protocol has been corrected accordingly.
Line 327 : "**Average Number of Steps**[14]: The average number of steps taken during the previous months will be collected using the GARMIN connected bracelet and reported by the participant during telephone calls at 2 months, 4 months and 6 months."

• Line 265: Please add how are technical problems with the app dealt with during the intervention? Are these recorded to further improve the usability of the app?

During the intervention, if a problem occurs, the patients call us directly and we try, together with the Opénium company's development engineers, to solve the problem within the day so as not to impact on the progress of the study. These problems are recorded by the company so that it can respond quickly if they recur.
Line 275: "If an issue with the app arises, patients are asked to contact us directly so that we can resolve the problem with the development engineers, if necessary, within the same day to avoid impacting the progress of the study."

• Line 396: unpaired t-test
Thank you. The correction was made on line 415.

• Line 430ff.: Is there a publication on the results of the predecessor / pilot study?
Thank you for your comment. We are in the process of publishing the results of the pilot study.

Reviewer: 3
Mr. Joseph Weddell, The University of Sydney

Comments to the Author:
Thank you for the opportunity to review the protocol for this important and interesting trial. The manuscript is well written, comprehensive and clearly thought out. I have some minor feedback to give you that you may wish to consider:

Page 6, line 133 - the word "be" is missing after "will" and before "blinded"
Thank you for your comment. The correction has been made.
Line 142 : "The assessor conducting the final study evaluation will be blinded to the participants' group allocation."

Page 7, exclusion criteria - I am just wondering what is the rationale behind excluding pregnant women in this study? It may be worth briefly clarifying.
We have added clarification concerning pregnant women.
Line 161: “We will not recruit pregnant women, as some of the exercises in this study may not be suitable for them, and we aim to avoid incomplete participation due to childbirth.”

Page 8, line 204 - are you also collecting marital/partner status in the sociodemographic data? Being married or partnered has been associated with higher adherence to exercise prescriptions/programs in other conditions and it may be worth considering the impact of this in your manuscript.
Thank you for this constructive advice. Indeed, we collect marital/partner status and we will consider this factor in our analysis.

Page 10, line 269 - you note that the control group will receive a booklet with a series of exercises designed to relieve pain, and then state that randomisation to the control group "will not change the daily life and activities of the participants." As you cannot definitively say that the care received in the control group (i.e. booklet) will or will not impact some change to daily life or activities, I would suggest rewording to something along the lines of "the control group will receive standard care, which in France consists of a booklet that..." etc
Thank you for your comment. We agree that this needs to be clarified.
We've reworded the text to reflect your comments.
Line 280: “The control group will receive standard care, which in France consists of an educational booklet that includes recommendations for physical exercises, such as strengthening, stretching, and aerobic exercises. The booklet also provides information on knee anatomy, weight loss, and both medical and non-medical treatments, including the use of braces and walking aids.”

Page 12, line 287 and page 15, line 444 - "barriers and levers", by which you mean barriers and facilitators (as noted in the same section) - is the word "lever" commonly used for "facilitators"? I have not come across the word "lever" used in this context before, and I would change it for facilitators unless it is the official name for this tool.
We agree that 'lever' was not a suitable word. We have removed it, and corresponding changes have been made throughout the manuscript to accurately reflect the nomination of the EPPA questionnaire.
Line 304 : “**Evaluation of the Perception of Physical Activity (EPPA)**[5,22]: The EPPA questionnaire will be used to assess barriers and facilitators to physical activity.”

Page 15, line 444 - the secondary outcomes of this study are worded a little unclearly in this passage, i.e. "thanks to pain levels", "barriers and leavers" and "the medico-economic section". Please could you reword to clearly state the secondary outcome variables.
Thank you for this comment.
We have clarified the secondary objectives.
Line 477-481 : “The secondary objectives of this study will also make it possible to determine whether the patient has gained in quality of life, thanks to the reduction in pain, a reduction in the score on the following self-questionnaires: EPPA, TSK, KOOS and EQ-5D-3L. This study will allow us to know if patients have gained joint mobility thanks to the goniometric measurement and if there is an increase in strength in functional tests.”

Pages 11,12 and 15 - for the included tools - have these tools been validated in studies with osteoarthritis populations? If so, please note this and provide citation(s).
The questionnaire EARS has not been validated in knee osteoarthritis. Evaluation of perception of physical activity has been validated in knee osteoarthritis by a team of Clermont Ferrand. The refrences have been noted in line 309 and 636. All the functional tests used in this study have been validated in knee osteoarthritis.

Thank you for the opportunity to review this well written protocol, and good luck with the trial.
Thank you for providing constructive comments that helped to improve our manuscript.

*** ***

COI statements:

Reviewer: 1
If you have selected 'Yes' above, please provide details of any competing interests.: None.

Reviewer: 2
If you have selected 'Yes' above, please provide details of any competing interests.: None.

Reviewer: 3
If you have selected 'Yes' above, please provide details of any competing interests.: None to disclose.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Liang, Shuang**
Affiliation	**The University of Sydney**
Date	**13-Dec-2024**
COI	

Thank you for the opportunity to review this protocol paper. The authors have thoroughly addressed most of the comments, resulting in a manuscript with significantly improved clarity. I would encourage the authors to include details on randomisation and allocation concealment, either in this paper or in a future publication of the main results. Incorporating this information will strengthen the study's methodological transparency and enhance its evaluation using tools like the RoB2, where these elements are important criteria for high-quality assessment. I wish the authors the best of luck with the trial and future research.