PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for SYNchronizing Exercises, Remedies in Galt and Cognition at Home (SYNERGIC@Home): Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia
AUTHORS	McGibbon, Chris; Jarrett, Pam; Handrigan, Grant; Bouchard, Danielle; Tranchant, Carole C.; Sexton, Andrew; Yetman, Linda; Robinson, Bryn; Crapoulet, Stephanie; Chamard-Witkowski, Ludivine; Liu-Ambrose, Teresa; Middleton, Laura; Almeida, Quincy; Bherer, Louis; Lim, Andrew; Speechley, Mark; Kamkar, Nellie; Montero Odasso, Manuel

VERSION 1 – REVIEW

REVIEWER	Öhlin, Jerry Umeå Universitet, Community Medicine and Rehabilitation
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	The authors present an interesting and pertinent feasability trial involving cognitive and physical training to improve gait and cognition. I find the methodology sound and the trial well documented.Their primary analytical outcome of the impact of preference on adherence is very interesting and will be a valuable addition to the field. I have some suggestions for improvement stated below. I refer to the page numbers on the top of the page, as the ones on the bottom are not sequential. Page 4, row 46: How many sessions/week? Page 4, row 63: Consider adding keyword regarding video conference training, as I believe it is an important part of this study and should be represented in the keywords, if possible. Page 6, Row 91-114, Introduction: Concise and effective introduction. Could be improved by adding the importance of individual preference on adherence to a intervention delivered via video conference, by relating it to previous studies on preference and adherence in traditional clinical trials. Page 12, Row 313: how will you choose participants for the mixed methods approach? Can you reach saturation with a fixed number of included participants? Page 13, row 338: This is not quite clear to me. Will the events be classified as AE, SAE and then if they were mild, moderate or severe, so for example, a SAE could be moderate? Or will they be classified as mild, moderate or severe adverse events? Page 17, row 485: I would like to see some more recent studies than those currently cited. Page 94, row 14: I can't agree that actigraphs can accurately measure sleep patterns, as they do not measure if the participant in fact are sleeping, or lying awake at night. This is especially

	important as sleep deprivation is common in this age group. Consider the term inactivity. Page 105, row 26: Perhaps Lawton-Brody IADL scale is better suited under the heading “Functional and activity level”? Page 109. Row 25: “A mixed a methods approach”, row 31: both comma and period at the end of the paragraph. Page 110, row 48: The relationship between intervention preference and adherence is a primary objective for the study, therefore a validated scale should be used, if available. Page 111, row 24-28: Considering the inclusion criteria of MCI/SCI, I suspect some participant will have difficulties with measuring their own vitals and reporting them. The authors should plan for how they should handle these potential missing values. Perhaps looking at the correlation between measures done by the participants at home, and measures in the clinic? Page 112, row 41: Could the authors please specify if the Lawton-Brody IADL scale will be completed by the participants and/or relatives? Page 113, row 21: The authors should specify that the validation was done with older people in japan. Page 115, row 12: “…to the best of his/her.” Should it end with “capacity?” Page 116, row 23: In the reference cited, I could not find the "Work and Sleep Diary". Furthermore, judging from the name of the scale it involves work, which might not be applicable for participants in this study considering the inclusion criteria of 60-90 years. Page 117, row 15: The authors cite a study with a 7 point frailty scale. Page 118, row 18: It would be interesting to see if compliance/adherence is associated with the FACET scale. Page 118, row 49-53: How will the authors handle those that cant show the gait and mobility assessment to the research assistants? If the research assistant can't confirm that the participants perform according to procedure, will these participants be analysed separately? Page 119, row 51: I could not fint he manual of procedures in the documents. Page 130, row 45: Are there no french alternatives in the BAT condition? Page 192, row 3: The Case report forms seem to be missing.

REVIEWER	Lim, Wen Northern Health, Aged Care
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	This is a very well written, clearly articulated protocol looking at the feasibility of cognitive and physical training in a home based setting. The intervention is strictly speaking a sequential cognitive and physical training intervention rather than a synchronous or simultaneous intervention. This distinction is important in the literature-refer to Gavelin et al, Ageing Res Rev . 2021 Mar;66:101232. doi: 10.1016/j.arr.2020.101232.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

“The authors present an interesting and pertinent feasability trial involving cognitive and physical training to improve gait and cognition. I find the methodology sound and the trial well documented. Their primary analytical outcome of the impact of preference on adherence is very interesting and will be a valuable addition to the field.”

We thank the reviewer for their encouraging comments.

These comments and responses pertain to the manuscript (MS). Page and line #s refer to the redline (TrackChanges) MS.

“Page 4, row 46: How many sessions/week?”

We have included this in the revised abstract (MS: pg. 2, line 47).

“Page 4, row 63: Consider adding keyword regarding video conference training, as I believe it is an important part of this study and should be represented in the keywords, if possible.”

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We have added “remote delivery” and “videoconferencing” to the keyword list (MS: pg. 2, line 66).

“Page 6, Row 91-114, Introduction: Concise and effective introduction. Could be improved by adding the importance of individual preference on adherence to a intervention delivered via video conference, by relating it to previous studies on preference and adherence in traditional clinical trials.”

We now include a more detailed summary to emphasize need to acquire measures of adherence and preference (MS: pg. 4, lines 110-122).

“Page 12, Row 313: how will you choose participants for the mixed methods approach? Can you reach saturation with a fixed number of included participants?”

Purposive sampling (commonly used in qualitative research) will be used to select participants, to acquire a balanced representation of sex, language, and treatment arm. Based on prior experience, it is expected that saturation will occur with up to 5 per arm or 20 participants. We have clarified this in the manuscript (MS: pg. 10, lines 331-332).

“Page 13, row 338: This is not quite clear to me. Will the events be classified as AE, SAE and then if they were mild, moderate or severe, so for example, a SAE could be moderate? Or will they be classified as mild, moderate or severe adverse events?”

We have revised the language to be clearer. An SAE will be defined as an event that results in death, is life threatening, requires hospitalization or results in persistent significant disability. AEs will be classified as mild, moderate, or severe (MS: pg. 11, lines 357-359).

“Page 17, row 485: I would like to see some more recent studies than those currently cited.”

We have updated some older references and have added several new references.

These comments and responses pertain to the detailed Protocol (PRv5) attachment. Please note we have attached the most recent version of the Protocol (PRv8), which includes the TrackChanges revisions made in response to the Reviewer, where applicable. Page and line numbers

“Page 94 [PRv5: 34], row 14: I can't agree that actigraphs can accurately measure sleep patterns, as they do not measure if the participant in fact are sleeping, or lying awake at night. This is especially important as sleep deprivation is common in this age group. Consider the term inactivity.”

We agree with the reviewer that there are limitations to measuring sleep with actigraphy, however, our goals are to assess feasibility in this trial. For secondary feasibility outcomes, data loss rate (common with actigraphy) will be important to analyse. For

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secondary analytic outcomes, getting measures of effect size, MCID, etc. will also be important for future trials.

“Page 105 [PRv5: 45], row 26: Perhaps Lawton-Brody IADL scale is better suited under the heading “Functional and activity level”?”
We thank the reviewer for catching this. We have revised the table accordingly (PRv8: pg. 44).
“Page 109 [PRv5: 49]. Row 25: “A mixed a methods approach”, row 31: both comma and period at the end of the paragraph.”
Fixed (PRv8: pg. 47).
“Page 110 [PRv5: 50], row 48: The relationship between intervention preference and adherence is a primary objective for the study, therefore a validated scale should be used, if available.”
Although the concept of preference trials has been around since the 1990’s, these studies have focussed on trial designs and randomization schemes where preference is a treatment arm and not a measured outcome. Academic studies of preference assessment are mostly confined to economics and marketing, and not directly translatable to our application. As such, we do not believe there is a validated scale available.
“Page 111, row 24-28 [PRv5: 51]: Considering the inclusion criteria of MCI/SCI, I suspect some participant will have difficulties with measuring their own vitals and reporting them. The authors should plan for how they should handle these potential missing values. Perhaps looking at the correlation between measures done by the participants at home, and measures in the clinic?”
Each participant with MCI/SCI has a study care partner who can help ensure vitals are measured properly. The study care partner is described in section 5.2.4 of the detailed protocol (PRv8: pg. 39).
“Page 112, row 41 [PRv5: 52]: Could the authors please specify if the Lawton-Brody IADL scale will be completed by the participants and/or relatives?”
The test is administered by the Research Coordinator with the participant. Participants with a care partner may have the partner to assist with the completion of this and any other assessments they require assistance for.
“Page 113, row 21 [PRv5: 53]: The authors should specify that the validation was done with older people in Japan.”
Many of our cited papers come from abroad.
“Page 115, row 12 [PRv5: 55]: “…to the best of his/her.” Should it end with “capacity?””
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Fixed (PRv8: pg. 52).
“Page 116, row 23 [PRv5: 56]: In the reference cited, I could not find the "Work and Sleep Diary". Furthermore, judging from the name of the scale it involves work, which might not be applicable for participants in this study considering the inclusion criteria of 60-90 years.”
We thank the reviewer for pointing this out. We mistakenly cited the Consensus Sleep Diary. The Work and Sleep Diary is a customized tool used by members of the research team. The instrument was chosen because some participants within our age (60-90 years old) range may still be in the work force or have formal volunteer work commitments so it will be important to capture work in this population. We have corrected this in the main protocol (PRv8: pg. 140).
“Page 117, row 15 [PRv5: 57]: The authors cite a study with a 7 point frailty scale.”
Although the original Clinical Frailty Scale (CFS) published by Rockwood [CMAJ. 2005;173(5):489-495] is a 7-point scale, the CFS used in clinical practice has two additional levels (8 and 9) related to bedridden patients and those in hospice care (https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html). The physical requirements of the study would exclude individuals at those levels of frailty; therefore, the validated 7-point instrument is effectively what we will be using.
“Page 118, row 18 [PRv5: 58]: It would be interesting to see if compliance/adherence is associated with the FACET scale.”
Indeed, we look forward to studying these relationships.
“Page 118, row 49-53 [PRv5: 58]: How will the authors handle those that cant show the gait and

mobility assessment to the research assistants? If the research assistant can't confirm that the participants perform according to procedure, will these participants be analysed separately?"
A requirement to participate in the study is being able to communicate and interact with the research coordinators and assistants using internet-based videoconferencing (Zoom). During screening procedures, which are also completed as virtual face-to-face meetings over Zoom, there will be ample opportunity to determine if technical difficulties will prevent enrollment in the study. As such, we have no plans presently to stratify the sample, however, we are tracking data loss as part of our feasibility outcomes (PRv8: pg 47; MS: pg 10, lines 317-322).
"Page 119, row 51 [PRv5: 59]: I could not fint he manual of procedures in the documents."
We did not intend to submit the manual of procedures.
"Page 130, row 45 [PRv5: 70]: Are there no french alternatives in the BAT condition?"
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The protocol appended was for the main anglophone site. The protocol for the francophone site contains the appropriate French content.
"Page 192, row 3 [PRv5: 132]: The Case report forms seem to be missing."
Case report forms (CRFs) contain many licensed instruments that we are not permitted to share, and therefore we have excluded the CRF package.
Reviewer: 2
"This is a very well written, clearly articulated protocol looking at the feasibility of cognitive and physical training in a home based setting."
We thank the reviewer for their encouraging comments.
"The intervention is strictly speaking a sequential cognitive and physical training intervention rather than a synchronous or simultaneous intervention. This distinction is important in the literature-refer to Gavelin et al, Ageing Res Rev 2021 Mar;66:101232. doi: 10.1016/j.arr.2020.101232."
We appreciate the reviewer's suggestion and have added a sentence to make this distinction clear (pg. 5, lines 140-142) and include a reference to the Gavelin paper.

VERSION 2 – REVIEW

REVIEWER	Öhlin, Jerry Umeå Universitet, Community Medicine and Rehabilitation
REVIEW RETURNED	02-Mar-2022

GENERAL COMMENTS	Greetings, The authors have adressed all my questions and concerns, and I can recommend this paper for publication. I am looking forward to the results from the finished trial.