PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the PreventIT randomised controlled trial feasibility study of a lifestyle-integrated exercise intervention in young older adults
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VERSION 1 – REVIEW

REVIEWER	Reviewer name: Wendy Katzman Institution and Country: University of California San Francisco Competing interests: None declared
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	This manuscript titled " Protocol: The PreventIT Feasibility RCT comparing two lifestyle-integrated exercise interventions delivered by use of ICT or an instructor with a control group in young older adults" describes the protocol for a multi-center 3-armed feasibility randomized controlled trial. The purpose is to determine the feasibility of enrolling young older adults (aged 61-70 years old) to an integrated life-style intervention in 2 modes versus a control group. The primary aim is to assess feasibility of the 2 interventions and a secondary aim is to determine effect size for sample size and design of a future clinical trial. The researchers have developed an Adapted LIFE (aLIFE) and Enhanced LIFE (eLIFE) program based upon the previous LIFE study and workshops and pilot testing within the PreventIT-consortium of researchers, exercise instructors and potential end-users. The aLiFE program has been pilot tested, and the eLife program is currently being pilot tested. The manuscript is generally well-written with detailed descriptions of most protocols. There are several areas that would benefit from further clarification. 1. Introduction (p.1) – interventions need to target each person's medical co-morbidities as well. 2. Introduction (p.1) – Please clarify this sentence: The LiFE programme includes strategies to improve balance and strength, where several principles are by suggestions for exercises. 3. Objectives (p.2) - You mention 24 months here but nowhere else in the manuscript. Please clarify.

	4. Methods (p.5) – what are the global activity recommendations you will provide to the control group? 5. Methods (p.5 and p.6) – how will you define “at risk” for functional decline as a risk-screening criteria? 6. Recruitment and randomization (p.5) – what type of registries are these? General census registries? 7. Web-based randomization (p.6) – please clarify that you will be providing a smart phone to those with none and who will train, how will they be trained and when will these participants be trained to use a smart-phone. 8. Instructors (p.7) – please describe the observation; ie: what criteria will be used to ensure fidelity and how many times will they be observed? 9. Complexity matrix (p.8) - There is an instance where the authors describe protocols that “could be implemented” when describing the complexity matrix that will be developed during the project. This is vague and would benefit from further clarification what data will be monitored. Also, will an individual’s home computer be monitored to collect data on social networking? 10. Secondary outcomes (p.9) – Please describe why you are using self-administered mobility and functional strength testing rather than by the trained tester. 11. Behavioral automaticity index (p.10) – why isn’t the control group completing this questionnaire? 12. Data storing and security (p.12) – Is data backed up on the server? 13. Smartphone (p.12) - Will individuals with an Apple-based phone be given an Android and if so, will they be considered in the Web-based randomization (see #9 above)? 14. Plans for dissemination of results?

REVIEWER	Reviewer name: Eliza Miller Institution and Country: Murdoch Children's Research Institute Australia Competing interests: None declared
REVIEW RETURNED	06-Jul-2018

GENERAL COMMENTS	This is a very detailed study protocol on a randomized controlled trial comparing the aLiFE and eLiFE programs. This work is an important step in determining the usability, acceptability and the lasting impacts of such programs in 'real-world' settings. Introduction: The introduction is reasonably well written however, there is a strong emphasis in the first paragraph on the disparity of health between men and women as they age. I felt this was not required when the study recruits both male and female young older adults. It felt as though the authors were building a case for recruiting only females in the study which was not the case.

	I question the number of participants in the current pilot of the eLiFE program and would consider more than fifteen participants are required to obtain comprehensive feedback on the usability of the eLiFE program. Although not technically part of this protocol review I would recommended extending the piloting of the eLiFE program in order to recruit more participants. The eLiFE program pilot is also half that of aLiFE with no justification on the reasons why. This should be included. The aim and objectives of the work are clear. Objective 3: Measuring the risk reduction of functional decline by the Later Life Function and Disability Instrument is important however I would recommend including here in the text that you will also collect mobility and functional strength change information from the participants. These measures offer important information on the effectiveness of the two interventions and should not be overlooked as they are an important aspect of the data collection. Objective 4: I commend the authors on including a Health economic evaluation, a vital but often overlooked aspect of research. Methods: The methods section is comprehensive, lengthy and sufficiently detailed to be repeated. The authors have done an excellent job including the level of detail that they have in this section. Recruitment and randomisation: The recruitment strategies for this study are well thought through and authors should be commended on their efforts to include a diverse age range of participants within their sampling frame of 61-70 years. There is no discussion of limitations in the study design. This is an important part of critically analysing research and should have been included. During the minor revision stage I recommend including a short paragraph on some of the study limitations for example- functional decline can begin much earlier in adult life than in the years of 60-70, why was the age range of 61-70 chosen? It appears that only retired young older adults are eligible the study, is this the case? If yes, why would you only consider inviting those who are retired to participate. The e and aLiFE program has the potential to offer immeasurable benefit to all of society including those still in the work force. Assessing its acceptability, maintenance and adherence in a working population is just as important. I commend the authors on the design of this RCT and can see the real world value following phase 3 of such a study however for this manuscript there are certain aspects which need to be revised. I recommend major revisions be made after consideration of the above feedback, specifically, a discussion section and discussion on the limitations need to be included along with a conclusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1:

“Introduction (p.1) – interventions need to target each person’s medical co-morbidities as well.”

Response 1: We agree with you in principle. However, our interventions do not focus on specific morbidities in older adults with known co-morbidities. We have therefore not changed the introduction but clarified why we focus on our target group.

Comment 2:

“Introduction (p.1) – Please clarify this sentence: The LiFE programme includes strategies to improve balance and strength, where several principles are by suggestions for exercises.”

Response 2: This sentence was part of the supplementary file containing an older version of the protocol for ethical approval of the study. It is not part of the introduction of the protocol manuscript, therefore we have not made changes.

Please see pages 25-26 under “Interventions” for a description of the intervention components.

Comment 3:

“Objectives (p.2) - You mention 24 months here but nowhere else in the manuscript. Please clarify.”

Response 3: The 24 months are only mentioned in the older document sent to the ethical committee that we uploaded as a supplementary file. We sincerely apologize for this confusion and have removed the supplementary file. The 24 months is only relevant for the objective five, where we will make a health economic model that can be used beyond the final assessment at 12 months. In the protocol paper, we have specified that our trial is a multicentre randomised controlled feasibility trial consisting of a 6-month intervention period post-randomisation and a further 6-month passive observational period. In total, participants are followed for 12 months post randomisation.

Comment 4:

“Methods (p.5) – what are the global activity recommendations you will provide to the control group?”

Response 4: In the protocol paper, we have described what the control group receives in more detail. Please see page 32 for details. We have a reference for the WHO recommendations of physical activity (line 2 of the section on page 32, reference number 54 in the manuscript) for clarification.

We have added the following sentence to page 32 to be more clear about the content: “These guidelines are relevant to all healthy older adults unless specific medical conditions indicate the contrary and highlight the benefits of being physically active as well as stimulate the recommended amount of physical activity to be undertaken per week.”

Comment 5:

“Methods (p.5 and p.6) – how will you define “at risk” for functional decline as a risk-screening criteria?”

Response 5: Thank you for pointing out this important question. In the protocol paper, we have explained in depth the term “at risk”. Please see the section at page 13 in the submitted protocol paper.

Comment 6:

“Recruitment and randomization (p.5) – what type of registries are these? General census registries?”

Response 6: The “local and regional registries” is described in more detail on page 10 under “eligibility criteria”: “Persons within the target group were randomly selected from three local population registries (The National Registry in Norway, the Municipality Registry of Amsterdam, and the Stuttgart Registry in Germany).”

Comment 7:

“Web-based randomization (p.6) – please clarify that you will be providing a smart phone to those with none and who will train, how will they be trained and when will these participants be trained to use a smart-phone.”

Response 7: Done as suggested. Please see:

- Table 5 (page 25), where the eLiFE participants with no prior smartphone experience will receive an extra home visit prior to starting the home visits in week 1.

- On pages 25-26 under “Interventions”, we have added the sentence: “eLiFE participants receive android phones that they use during the intervention and follow-up period. Participants without any smartphone experience receive one extra home visit with information on how to use a smartphone prior to starting the home visits in week 1.”

Comment 8:

“Instructors (p.7) – please describe the observation; ie: what criteria will be used to ensure fidelity and how many times will they be observed?”

Response 8: In the final protocol, this is clarified in the following way on page 32 (three lines at the end of the section “eliFE/aLiFE instructors”): “All instructors were tested and awarded certification prior to the start of the study, to ensure that they had the competences needed to deliver both the eLiFE and the aLiFE interventions.”

Comment 9:

“Complexity matrix (p.8) - There is an instance where the authors describe protocols that “could be implemented” when describing the complexity matrix that will be developed during the project. This is vague and would benefit from further clarification what data will be monitored. Also, will an individual’s home computer be monitored to collect data on social networking?”

Response 9a: We thank the reviewer for commenting on this. In the submitted protocol paper we have described the complexity metric in more detail, please see:

- Abstract, page 3, “…and a physical behaviour complexity metric.”

- Aims, page 9, under objective 4: “and the behavioural complexity metric”

- Methods, page 14: “and a complexity metric (20), further developed and adapted within the project to assess behavioural complexity in the domains of physical activity, sleep, and social participation.”

• Methods, page 14-15, where a separate section describes the measure in more details, starting with “Physical activity and sleep data..” at the end of page 14 and ending with “…less complex physical behaviour (32)” at the first section of page 15.

Response 9b:

Data on social networking will be not collected from the individual’s home computer. Instead, we will use data from the individual’s smartphone and physical activity monitored with the wearable sensor, as described in section Methods, page 14:

“Assessment on social interaction is based on detection of outdoor walking derived from the timing and the number of steps of walking episodes. Frequency and number of SMSs and phone calls and GPS statistics are also used as possible social interaction measures. These statistics are anonymous, without identifying the caller/sender”.

Comment 10:

“Secondary outcomes (p.9) – Please describe why you are using self-administered mobility and functional strength testing rather than by the trained tester.

Response 10: The self-administered tests of mobility, balance and functional strength are used in addition to the standard outcome measures test battery that are performed by the trained testers. Only data from the latter standardized tests will be used to test for change (objective 4). Please see page 15 in the submitted protocol paper, where we have described this in more detail. The self-administered tests are part of the PreventIT project to evaluate acceptability of such tests. Please see Table 3 (pages 16-23) where all outcome measures are described and referenced.

Comment 11:

“Behavioral automaticity index (p.10) – why isn’t the control group completing this questionnaire?”

Response 11: Thank you for pointing out that this was not clear. In the protocol paper, we have added Table 3 where all measures are described and references included, please see page 21 for the behavioural automaticity index part. All three treatment arms are asked to complete the behavioural automaticity index questionnaire at 6 and 12 months post-randomisation.

Comment 12:

“Data storing and security (p.12) – Is data backed up on the server?”

Response 12: Please see the detailed description on page 36 under “Data storing and security.” Where we have added: ”Data are synched daily from the smartphones onto the servers. Moreover Data on the servers are backed up daily as part of the routine scheduled backup of the NTNU computer center that hosts the PreventIt servers.”

Comment 13:

“Smartphone (p.12) - Will individuals with an Apple-based phone be given an Android and if so, will they be considered in the Web-based randomization (see #9 above)?”

Response 13: Yes, participants with an Apple-based phone will be given an Android phone. Please see our responses to comments 7 and 9 above. We have added a sentence in the manuscript for clarification: “eLiFE participants receive android phones that they use during the intervention and follow-up period. Participants without any smartphone experience receive one extra home visit with information on how to use a smartphone prior to starting the home visits in week 1.” (pages 25-26 under “Interventions”)

Comment 14:

“Plans for dissemination of results?”

Response 14: The dissemination policy is described in a separate section, see pages 36-37, where the following is described: “We will seek to publish all results from the feasibility trial in open access, peer-reviewed international journals, and disseminated at scientific and non-scientific conferences and events. Main results will also be shared on the project website and spread to various stakeholders. Authorship eligibility will follow ICMJE (International Committee of Medical Journal Editors) (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).“

Reviewer: 2

Comment 1:

“Introduction: The introduction is reasonably well written however, there is a strong emphasis in the first paragraph on the disparity of health between men and women as they age. I felt this was not required when the study recruits both male and female young older adults. It felt as though the authors were building a case for recruiting only females in the study which was not the case.”

Response 1: Thank you for pointing this out. We agree, and in the protocol paper the introduction is rewritten without the same focus on genders.

Comment 2:

“I question the number of participants in the current pilot of the eLiFE program and would consider more than fifteen participants are required to obtain comprehensive feedback on the usability of the eLiFE program. Although not technically part of this protocol review I would recommended extending the piloting of the eLiFE program in order to recruit more participants. The eLiFE program pilot is also half that of aLiFE with no justification on the reasons why. This should be included.”

Response 2: The number of participants in two earlier pilot studies was described in an earlier document for the ethical committee only, which was attached as a supplementary file. As this led to confusion, we have removed the ethical application document. The pilot studies were conducted in 2016 and their results used to fine-tune the interventions that are described in the current protocol paper for the feasibility RCT.

Comment 3:

“The aim and objectives of the work are clear.

Objective 3: Measuring the risk reduction of functional decline by the Later Life Function and Disability Instrument is important however I would recommend including here in the text that you will also collect mobility and functional strength change information from the participants.These measures offer important information on the effectiveness of the two interventions and should not be overlooked as they are an important aspect of the data collection.

Objective 4: I commend the authors on including a Health economic evaluation, a vital but often overlooked aspect of research.”

Response 3: Thank you for your appreciation for objective 4, and we fully agree with your comment on objective 3. Please see the full description of objectives in the protocol paper, where the estimates of change (objective 4) are described as follows: “What is the change in function, as measured by two primary clinical outcome measures: the Later Life Function and Disability Instrument (LLDFI) and the behavioural complexity metric, for the eLiFE and the aLiFE interventions compared to the control group? What are the estimated effect sizes for LLFDI, complexity metric, and the secondary clinical outcome measures?” (page 9). The secondary clinical outcome measures include several estimates of mobility and functional strength.

Please also see the response to the first comment from the editor, where we describe several changes that will make the manuscript more clear when it comes to the outcome measures in this trial.

Comment 3:

“Methods:

The methods section is comprehensive, lengthy and sufficiently detailed to be repeated. The authors have done an excellent job including the level of detail that they have in this section.

Recruitment and randomisation: The recruitment strategies for this study are well thought through and authors should be commended on their efforts to include a diverse age range of participants within their sampling frame of 61-70 years.

There is no discussion of limitations in the study design. This is an important part of critically analysing research and should have been included. During the minor revision stage I recommend including a short paragraph on some of the study limitations for example- functional decline can begin much earlier in adult life than in the years of 60-70, why was the age range of 61-70 chosen? It appears that only retired young older adults are eligible the study, is this the case? If yes, why would you only consider inviting those who are retired to participate. The e and aLiFE program has the potential to offer immeasurable benefit to all of society including those still in the work force. Assessing its acceptability, maintenance and adherence in a working population is just as important.

I commend the authors on the design of this RCT and can see the real world value following phase 3 of such a study however for this manuscript there are certain aspects which need to be revised. I recommend major revisions be made after consideration of the above feedback, specifically, a discussion section and discussion on the limitations need to be included along with a conclusion.”

Response 4: We are delighted with your positive comments, thank you. Regarding your comment about limitations, we agree. In the protocol manuscript, we have added a discussion part where we have raised some issues with the current trial. We have also made stronger justification of the age range in this group and why we have chosen this age range and retirement throughout the manuscript.

In addition to the changes described in this letter, we have done some small corrections of the text. We have also uploaded a new version of the flow chart (Figure 2), due to finding some small errors in the numbers in the different phases of the study trial.

Once again we thank the Editors and Reviewers for the constructive comments and suggestions. We hope we have responded adequately to your suggestions.

We have uploaded a revised manuscript, called “MainText_revision1”. Please notice that the pages we refer to in this response letter refer to this revised manuscript. We also upload one marked version where all track changes are shown, called “MainText_revision1_marked”.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Wendy Katzman Institution and Country: University of California San Francisco, USA Competing interests: None declared
REVIEW RETURNED	21-Sep-2018

GENERAL COMMENTS	This manuscript titled “Protocol for the PreventIT randomized controlled trial feasibility study of a lifestyle-integrated exercise intervention in young older adults” describes the protocol for a multi-center 3-armed randomized controlled trial feasibility study. The purpose is to determine the feasibility of enrolling young older adults (aged 61-70 years old) to an integrated life-style intervention in 2 modes versus a control group. The primary aim is to assess feasibility and usability, evaluate and improve the intervention, and to determine effect size for sample size for a future Phase III clinical trial comparing eLIFE and aLIFE interventions to a control group. The researchers developed an Adapted LIFE (aLIFE) and Enhanced LIFE (eLIFE) program based upon the previous LIFE study, workshops and pilot testing within the PreventIT-consortium of researchers, exercise instructors and potential end-users. The aLiFE and eLIFE programs have been pilot tested. The manuscript is well-written, with detailed descriptions of protocols, interventions and outcome assessment. I previously reviewed this manuscript and the authors have since pilot tested the eLIFE program and incorporated those results into this revised protocol. They adequately addressed all prior concerns, and I recommend this manuscript for publication.

REVIEWER	Reviewer name: Eliza Miller Institution and Country: Murdoch Childrens Research Institute Competing interests: None declared
REVIEW RETURNED	26-Sep-2018

GENERAL COMMENTS	I commend the authors on their commitment and efforts to improve this manuscript. The modifications they have made have improved this manuscript ten-fold. I look forward to reading a final published copy.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1: “This manuscript titled “Protocol for the PreventIT randomized controlled trial feasibility study of a lifestyle-integrated exercise intervention in young older adults” describes the protocol for a multi-center 3-armed randomized controlled trial feasibility study. The purpose is to determine the feasibility of enrolling young older adults (aged 61-70 years old) to an integrated life-style intervention in 2 modes versus a control group. The primary aim is to assess feasibility and usability, evaluate and improve the intervention, and to determine effect size for sample size for a future Phase III clinical trial comparing eLIFE and aLIFE interventions to a control group. The researchers developed an Adapted LIFE (aLIFE) and Enhanced LIFE (eLIFE) program based upon the previous LIFE study, workshops and pilot testing within the PreventIT-consortium of researchers, exercise instructors and potential end-users. The aLiFE and eLIFE programs have been pilot tested. The manuscript is well-written, with detailed descriptions of protocols, interventions and outcome assessment.

I previously reviewed this manuscript and the authors have since pilot tested the eLIFE program and incorporated those results into this revised protocol. They adequately addressed all prior concerns, and I recommend this manuscript for publication."

Reviewer: 2: "I commend the authors on their commitment and efforts to improve this manuscript. The modifications they have made have improved this manuscript ten-fold. I look forward to reading a final published copy."

Response to reviewers 1 and 2: We are delighted with your positive comments, thank you.

Once again we thank the Editor and Reviewers for the constructive comments and suggestions during the review process. We trust we have responded adequately to your suggestions.

We have uploaded a revised manuscript, called "MainText_revision2_041218" and a marked version with track changes, called "MainText_revision2_041218_marked".