

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Selective prevention of cardiovascular disease using integrated lifestyle intervention in primary care: protocol of the Healthy Heart stepped-wedge trial
AUTHORS	Bonten, Tobias N.; Verkleij, Sanne; van der Kleij, Rianne; Busch, Karin; van den Hout, Wilbert; Chavannes, Niels; Numans, Mattijs

VERSION 1 – REVIEW

REVIEWER	Rajeev Gupta Chair Preventive Cardiology and Medicine Eternal Heart Care Centre and Research Institute, Jaipur; India. Chair Academic Research Development Unit, Rajasthan University of Health Sciences, Jaipur; India
REVIEW RETURNED	17-Oct-2020

GENERAL COMMENTS	<p>General comments:</p> <ol style="list-style-type: none">1. This is an important piece of research as previous studies on multiple risk factor intervention for primary prevention in primary care have been inconclusive.2. Stepped wedge design is suitable but from the description it appears that is a clustered, stepped wedge design, please specify. An intervention is planned. How can this be called an observational study?3. However, I am concerned with the follow-up and intervention duration. 24 months is a very short time.4. Language needs better flow and overall improvement. <p>Specific comments:</p> <p>Abstract</p> <ol style="list-style-type: none">5. The Introduction section is very long. Most of the facts stated are well known and should be deleted.6. Please clarify the type of study. Observational vs interventional.7. A few details of stepped wedge design, type of intervention, etc, should be provided.8. The primary outcome is achievement of individual lifestyle goals. Why, then, the same are included in the secondary outcomes?9. What is RE-AIM model?10. What are the possible conclusions? <p>Article summary:</p> <ol style="list-style-type: none">11. Please be clear of the type of study.12. Clustered randomized trial is also a method of performing a randomized trial. In the early phase more than 90% are not in interventional arm and act as controls. Over the time period more and more are included in intervention, so finally you have a balanced controls and intervention participants.13. The summary statement includes a focus group discussion, This is qualitative component of the study and should also be mentioned in the abstract. <p>Background:</p>
-------------------------	--

	<p>14. This section is not clear. Please refer to previous studies on lifestyle interventions for risk factor modification. Multiple Cochrane reviews exist and should be cited.</p> <p>15. Aims and objectives are not clear and are different as compared to the abstract.</p> <p>Methods:</p> <p>16. In Setting section, please use future tense rather than the past tense.</p> <p>17. The last 2 lines of Setting section are not understandable.</p> <p>18. Study Population section states “primary care practices are asked to participate in this study of they offer the structured prevention program”. If the practices already offer a CVD prevention program, there is no sense of conducting the study as there is no clinical equipoise.</p> <p>19. Inclusion criteria of practices and participants should be more explicit.</p> <p>20. Why have you excluded diabetes patients with no CVD?</p> <p>21. Usual care section should be more detailed.</p> <p>22. Group Based Lifestyle Intervention section should have clear and detailed criteria for inclusion, training of providers, and components of the training.</p> <p>23. Measurements section is poorly worded. What is routine measurements? No other details are provided.</p> <p>24. Baseline questionnaire section should be before the intervention section. Please void back-and-forth statements.</p> <p>25. Details of follow-up methodology are missing.</p> <p>26. For an average reader, clustered design is new. Please describe here. A figure would be more useful in explaining the method.</p> <p>27. Implementation section introduces a new component- mixed-methods process evaluation. This has not been mentioned in the abstract or summary.</p> <p>28. Very broad concepts are presented in this section. Please describe the methods that you would use for implementation.</p> <p>29. Cost-effectiveness section is not well written. Again generalizations are provided with no focus on the study itself.</p> <p>30. Would there be a need to include indirect costs?</p> <p>31. Sample size calculations are based on number of participants and not clusters. Please clarify.</p> <p>32. Is a 5% difference absolute or relative?</p> <p>Statistical analyses:</p> <p>33. The first statement suggests a case-control design and not stepped wedge design. Please clarify.</p> <p>34. You would determine the outcome interventions at 6 month of intervention. Then why the follow-up up to 24 months. Evaluation of legacy effects?</p> <p>35. Discussion:</p> <p>36. Very poorly written and not relevant to the study question.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Response to comments of the reviewer:

1. *Stepped wedge design is suitable but from the description it appears that is a clustered, stepped wedge design, please specify. An intervention is planned. How can this be called an observational study?*

We agree with the reviewer that this point is unclear. An intervention (offering a group-based lifestyle program) is planned, so the study can be called a (non-randomized) trial indeed. We have adapted this throughout the manuscript.

2. *However, I am concerned with the follow-up and intervention duration. 24 months is a very short time.*

We agree with the reviewer and would have preferred a longer follow-up. However, the follow-up duration corresponds to many previous intervention studies in this field and most important lifestyle changes can be observed in this period. For example, the mean treatment duration of weight reduction trials in hypertensive patients was 6 to 36 months.(Semlitsch T, et al. Cochrane Database Syst Rev. 2021 Feb 8;2:CD008274.). Also, the median follow-up duration of trials investigating multiple risk factor interventions for primary prevention of coronary heart disease was 12 months, whereas our follow-up duration is 24 months.(Ebrahim s, et al. Cochrane Database Syst Rev.2011 Jan 19;(1):CD001561.)

Still, a recent meta-analysis showed that lifestyle intervention in subjects at high cardiovascular risk (n= 6350) resulted in none to only a modest effect on systolic blood pressure and no effect on total cholesterol after 24 months.(Bergum H, et al. BMC Cardiovasc Disord. 2021 Apr 15;21(1):181.)This substantiates the importance of long-term follow-up in lifestyle trials benefits to ensure impact on cardiovascular outcomes.

Importantly, to study the implementation of a lifestyle intervention at practice level, the time of 24 months is sufficient in our opinion.

We added this point to our discussion (pge 21)

3. *Language needs better flow and overall improvement.*

We reviewed the manuscript and improved language where necessary.

Abstract:

4. *The Introduction section is very long. Most of the facts stated are well known and should be deleted.*

We have shortened the introduction of the abstract to, in our opinion, a readable and to-the-point text.

5. *Please clarify the type of study. Observational vs interventional.*

We have clarified this point and also refer to our answer to comment no. 1.

6. *A few details of stepped wedge design, type of intervention, etc, should be provided.*

We have now added a few sentences about this part of the manuscript to the abstract.

7. *The primary outcome is achievement of individual lifestyle goals. Why, then, the same are included in the secondary outcomes?*

We have chosen to assess achievement of combined lifestyle goals as the primary endpoint, because we did not want to prioritize only one lifestyle component as primary outcome. This also substantiates the integrated nature of the intervention. From our experience in clinical practice and previous lifestyle literature, we are of opinion that much lifestyle studies are restricted to only one or two components. However, we also are interested in studying individual components and facilitate comparison with previous literature on those components.

We have added this clarification to the manuscript (page 17)

8. *What is RE-AIM model?*

We apologize for not clarifying this method in the abstract. The RE-AIM model is a well-known model to evaluate public health interventions that assesses 5 dimensions: reach, efficacy, adoption, implementation, and maintenance. These dimensions occur at multiple levels (e.g., individual, clinic or organization, community) and interact to determine the public health or population-based impact of a program or policy.

We have now added a short explanation to the abstract as follows:

“Implementation outcomes will be assessed using the RE-AIM model, to assesses 5 dimensions of implementation at different levels of organization: reach, efficacy, adoption, implementation, and maintenance. “

9. *What are the possible conclusions?*

Possible conclusions are the an integrated lifestyle program in primary care is a cost-effective intervention to improve lifestyle and thereby cardiovascular risk in a high risk population. This heading is not a standard paragraph in the BMJopen abstract format, so we did not add this to the abstract in our revised version.

Summary:

10. *Please be clear of the type of study.*

We have now clarified the type of study.

11. *Clustered randomized trial is also a method of performing a randomized trial. In the early phase more than 90% are not in interventional arm and act as controls. Over the time period more and more are included in intervention, so finally you have a balanced controls and intervention participants.*

We agree with the reviewer here. Still, we chose to discuss the possible disbalance of baseline variables as a limitation, because different patients may visit the GPs over time.

12. *The summary statement includes a focus group discussion, This is qualitative component of the study and should also be mentioned in the abstract.*

We agree with the reviewer and now added this important aspect of our implementation study to the abstract (page 3):

“Determinants of adoption and implementation will be assessed through focus groups with professionals and patients.”

Background:

13. *This section is not clear. Please refer to previous studies on lifestyle interventions for risk factor modification. Multiple Cochrane reviews exist and should be cited.*

We have now clarified this section and added multiple references citing lifestyle intervention studies.

14. *Aims and objectives are not clear and are different as compared to the abstract.*

We have clarified the aims paragraph. The text in the abstract and background section on this point is now comparable.

Methods:

15. *In Setting section, please use future tense rather than the past tense.*

We have corrected this to future tense.

16. *The last 2 lines of Setting section are not understandable.*

We apologize for the unclarity of these sentences. We corrected this as follows:

“ The lifestyle program will be implemented in the participating primary care practices as part of routine care . As a result, recruitment of patients will be initiated in primary care practices connected to the care group and not through recruitment by the research team. (pge 7).

17. *Study Population section states “primary care practices are asked to participate in this study of they offer the structured prevention program”. If the practices already offer a CVD prevention program, there is no sense of conducting the study as there is no clinical equipoise.*

We think there is still equipoise in the fact that we do not know whether offering an integrated lifestyle program **on top of** routine care with structured CVD prevention provides any benefit and is cost-effective. We have clarified this as follows (pge 8):

“Primary care practices are asked to participate in this study if they already offer the structured CVD prevention protocol, which is usual care in The Netherlands.”

18. *Inclusion criteria of practices and participants should be more explicit.*

We have now made inclusion criteria explicit (pge 8)

19. *Why have you excluded diabetes patients with no CVD?*

Since they are already selected for the diabetes mellitus structured primary care protocol, respectively. Also, the lifestyle intervention program is not reimbursed for diabetic patients without CVD at the time the study starts.(pge 9)

20. *Usual care section should be more detailed.*

We have now added more details about usual care, which is the standard cardiovascular preventive care in the Netherlands.(pge 10)

21. *Group Based Lifestyle Intervention section should have clear and detailed criteria for inclusion, training of providers, and components of the training.*

We have clarified this as follows (pge 10 and 11):

Only Lifestyle coaches who are certified and trained by the Dutch Association for Lifestyle Coaches are included in this study. All lifestyle coaches in this project are members of the Professional Association of Lifestyle Coaches in the Netherlands. They completed a post-graduate training course in lifestyle coaching at the Dutch Academy for Lifestyle and Health.

The detailed components of the training are now provided as a supplemental table (S1).

22. *Measurements section is poorly worded. What is routine measurements? No other details are provided.*

We have now reworded the section and hope to have improved the reading here.

23. *Baseline questionnaire section should be before the intervention section. Please void back-and forth statements.*

We agree with the reviewer that switching this section contributed to the readability of this section. We have also deleted back-and-forth statement.

24. *Details of follow-up methodology are missing.*

Follow-up measurements are now clearly depicted at page 13.

25. *For an average reader, clustered design is new. Please describe here. A figure would be more useful in explaining the method.*

We agree with the reviewer that the clustered design might be new to readers, although it is often applied in primary care studies. We designed several figures to clearly present the design of this study to readers, which resulted in figure 1. Adding complexity to this figure with visual representation of clusters and the stepped-wedge design did not result in a clear figure in our opinion. To address the concerns of the reviewer, we have now added an explanation of a clustered design to the methods section (pge 6):

“We designed this study as clustered trial, which means that the intervention is implemented on the level of a general practice instead of on the level of an individual participant.”

And also added words the title of figure 1 and throughout the methods section.

26. *Implementation section introduces a new component- mixed-methods process evaluation. This has not been mentioned in the abstract or summary.*

We apologize for this mistake and now added this method to the abstract and summary.

27. *Very broad concepts are presented in this section. Please describe the methods that you would use for implementation.*

We have now made this section more concrete by adding text (pge 14):

“The primary care group Hadoks implements the lifestyle intervention program in the primary care practices. Concretely, this is done by a staff nurse specialized in cardiovascular disease during a start meeting in every primary care practice. During this start meeting, the GP, practice nurse and lifestyle coach are educated about the start and content of the program and instructed about referral logistics and registration for the study. During the program, the staff nurse is available for feedback and questions concerning the lifestyle program or research study, supported by the Healthy Heart study team.”

28. *Cost-effectiveness section is not well written. Again generalizations are provided with no focus on the study itself.*

We have now clarified some of the text here. It is important to mention that the methods described are advised by a health economist and are focussed on this study. In our opinion, the adapted text is now clear and with enough focus on the study without providing too much detail about the methods itself, which are standard methods used in cost-effectiveness analyses, and making this section too long for the reader.

29. *Would there be a need to include indirect costs?*

We agree with the reviewer that it would be informative to add indirect costs to the analysis. We added the following text to the manuscript (page 15):

“A cost price analysis will be performed for the group-based intervention using data from the primary care group Hadoks, also including indirect costs that are not directly related to patient care (administration, physical room for group sessions and human resources and practice and primary care group level).

30. *Sample size calculations are based on number of participants and not clusters. Please clarify.*

We first calculated the required number of participants, then the required number of clusters and corrected the required sample size for the clustering effect. We have now added this to the text (page 16):

“With a sample size of 1600 participants, we can detect a difference of 5% between the control period and intervention period, with correction for clustering using a coefficient of variation between practices (clusters) of 0.4, with a power of 99% on a 5% significance level.”

We decided to calculate the required number of participants first, because the primary endpoint addresses the data on a participant level and not cluster level.

31. *Is a 5% difference absolute or relative?*

Absolute. We added this to the text (page 16): “With a sample size of 1600 participants, we can detect an absolute difference of 5%...”

Statistical analyses:

32. *The first statement suggests a case-control design and not stepped wedge design. Please clarify.*

We apologize for the unclarity here. The first statement describes the statistical tests used to compare baseline characteristics between participants in our prospective trial, and not a case-control study. We have now adapted the text as follows (page 17):

“Chi-squared tests for categorical variables and unpaired t-tests for continuous variables will be used to compare baseline characteristics of participants who are included during the control period with participants who are included during the intervention period”

33. *You would determine the outcome interventions at 6 month of intervention. Then why the follow-up up to 24 months. Evaluation of legacy effects?*

Yes. We are interested in studying lifestyle change. Of course, we know that long-term lifestyle change is the most relevant to study, many important previous studies used analysis

at 6 months follow-up as their main endpoint. To facilitate comparison with those studies we also chose to determine our main outcome at 6 months (short-term lifestyle change), but also analyse outcomes at 24 months (legacy- or long-term effects).

The reasoning is described in the manuscript (page 17):

“Achievement of lifestyle goals will be determined at six months, because this time window covers the duration of the lifestyle program, and it is a frequently used timepoint to assess the impact of lifestyle interventions.[1, 10]”

Discussion:

34. *Very poorly written and not relevant to the study question.*

We revised the discussion and tried to focus on relevance for the study question.

VERSION 2 – REVIEW

REVIEWER	Rajeev Gupta Chair Preventive Cardiology and Medicine Eternal Heart Care Centre and Research Institute, Jaipur; India. Chair Academic Research Development Unit, Rajasthan University of Health Sciences, Jaipur; India
REVIEW RETURNED	27-May-2021
GENERAL COMMENTS	1. The article now appears better. The language and flow has been improved and the article is much better. 2. There still are problems with the English grammar. I hope that these are corrected in the next stage.

VERSION 2 – AUTHOR RESPONSE

Response to comments of the reviewer:

There still are problems with the English grammar. I hope that these are corrected in the next stage.

We consulted a native speaker to address the English grammar and updated the manuscript accordingly.