Author’s response to reviews

Title: Design of the ZWOT-CASE study: an observational study on the effectiveness of an integrated programme for cardiovascular risk management compared to usual care in general practice

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Author’s response to reviews:

Dear Editor, dear Dr Lingling Tian,

Enclosed please find the second revised version of our manuscript entitled, “Design of the ZWOT-CASE study: an observational study on the effectiveness of an integrated programme for cardiovascular risk management compared to usual care in general practice” for consideration for publication as an study protocol paper in BMC Family Practice.

We appreciate the interest of the Editor and reviewers in our manuscript. We would like to thank the reviewers for their constructive feedback and helpful comments. By incorporating their remarks and suggestions we were able to optimize our manuscript. A point-by-point response to the comments of the reviewers appended to this letter. All changes in the manuscript are indicated in the text by using track changes.
In our view, the readership of the BMC Family Practice is the most appropriate audience to present our study protocol to; This paper is relevant for general practitioners and researchers in primary care across the world who wish to stay informed about cardiovascular primary care and to emphasize the importance of scientific evaluation of cardiovascular risk management.

Thank you again for consideration of our revised manuscript. We appreciate your time and are eagerly awaiting your response.

With kind regards,

On behalf of all co-authors,

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General comment: We would like to thank both reviewers for their constructive feedback and helpful comments for correction or modification. We believe that the changes further improved our manuscript.

Reviewer 1: Robert McKelvie, M.D., Ph.D
Comment:

Summary

This is a revised version of a previous submission. This is an observational study. The primary aim of the ZWOT-CASE study is to investigate whether the execution of an integrated primary care programme for CVRM in general practice leads to a more favourable CV risk profile in patients with known CVD or at high risk as compared to usual care. The authors have responded to the previous comments. I still have concerns about the design because it seems unnecessarily complex. They seem overly concerned about the Hawthorne effect so they want to follow the patients along with the physicians not knowing they are being observed. I am not sure this concern is as great as they are suggesting. However, if there is this concern it may have been better if they randomized in a step wedge fashion the physicians that were agreeable to be involved with the integrated primary care programme and just delay the time the involvement of some of the practices would start. However, ultimately they would all finally be involved in the integrated primary care programme. The fact one group wants to be involved in the integrative primary care programme and the other does not, for whatever reason, would seem to set the study up for a great deal of potential bias. The design will also set up a situation where there potentially will be a great deal of missing data. However, this is a design paper and my comments should not detract from the quality of the idea for this study. I think the question is important and this type of management strategy should be properly evaluated. However, I do think the paper is too long and would benefit by decreasing the length by at least 25% or so.

Answer: We understand the concerns of the reviewer about the design. However, we still think that our concerns about the Hawthorne effect are justified, as some earlier studies have shown. As we described in our answer on a previous comment, we expect that the effect of being aware of being in a study will not be equal in both groups and this would certainly lead to considerable bias. We also considered a stepped wedge cluster randomized trials, which was also suggested by the reviewer. In fact this is a design our group has used in earlier studies. Unfortunately, however, at the time we designed our study, the physicians just started the integrate care programme and it was not possible anymore to delay the time, let alone randomly allocate a time when practices would switch to the integrated care program. Moreover, stepped wedge trials have other important limitations such as the impossibility to add additional practices in case the number of inclusions is too low. Consequently, we considered and still consider, a controlled observational study the best approach. We are aware that also this design has methodological limitations, notably potential confounding. As described in our manuscript, measures have been taken (notably matching of patients, multivariable analyses) to prevent confounding in our study. We agree with the reviewer that there is a risk of missing data, especially in the control group at baseline, but missing data will occur in all studies and, importantly, the number of missings for the outcome parameter will be very small. We would further like to refer to page 17 where we described how we handle missing data in our study.
Finally, the reviewer suggests to reduce the length of the paper by around 25%. Consequently, we tried to decrease the length where possible. However, as this is a study protocol we think it is important to describe the design and intervention sufficiently precise to facilitate replication. The second reviewer asked for some more precise descriptions. Therefore, decreasing the length of the paper by as much as 25% was not quite possible.

Reviewer 2:

Comments:

1. This is the study protocol of an observational study of improving cardiovascular risk management in primary care in one regional network in the Netherlands. The trial has been registered and the study protocol is consistent with the information in registered trial protocol. The trial has been registered on 9 Feb 2018, while inclusion of practices and patients started in 2016. So, registration is retrospective rather than prospective. It is up to the journal to decide whether this is still acceptable. The study does not seem to include a process evaluation, although this is now common practice in evaluation of complex interventions.

Answer: We agree with the reviewer that it would have been more ideal to register the trial at study initiation. We support the importance of trial registration to increase the transparency and accountability of clinical research. We think that our retrospective registration at least ensures complete publication of all results.

We appreciate the reviewers comment on lack of a process evaluation. We agree this is an important part of evaluation of complex interventions. We are planning a process evaluation, but as we are still working on this, it is not described in the study protocol.

Introduction

2. The introduction does not relate to a large body of research in primary care in the Netherlands concerning the improvement of CVRM (e.g. from the universities in Maastricht, Nijmegen and Utrecht in the Netherlands). Likewise, published research on the chronic care model as applied to cardiovascular risk management has not been considered. Therefore, the study is not as well contextualized in the available body of research as it could have been.
Answer: We agree with the reviewer that many studies have been conducted on the improvement of CVRM in primary care in the Netherlands and in the earlier version of the manuscript we included a few of these. We added additional references in the revised manuscript (9, 10, 18, 19) that in our opinion are of added value to our study protocol. We focused citations on the most recent research that is strongly related to our research question. Additionally, we chose to cite some international studies (including reviews) as in our opinion these were very relevant for the rationale of our study.

3. The most relevant guideline for primary care in the Netherlands (NHG-standaard CVRM, reference 8) has recently been updated. The version of 2012 is no longer up to date. Also, the specific aims for improvement (p.5) should be checked against the new guideline.

Answer: We are aware of the updated version of the Dutch guideline for CVRM. However, this updated version has been published in May 2019 after the submission of our revised study protocol in April 2019 (and first submission in February 2018). However, we agree that it is important to refer to the updated version of the Dutch guideline for CVRM and added it to the reference list.

We agree with the reviewer that it is important to check the treatment goals in the new guideline. However, as this study was conducted from 2016 till 2018, the aims of the integrated care programme for CVRM were according to the previous guideline from 2012.

Methods

4. It is highly recommended to use reporting guidelines (and add these as appendices) for both the study design (e.g. STROBE) and a detailed description of the intervention (e.g. TIDIER).

Answer: We thank the reviewer for this suggestion and added both checklists (STROBE and TIDIER) as appendices.

5. Ethics approval is only presented on p.13, but should be presented upfront in the first paragraph of the methods section. A reference number or date of the approval letter needs to be given as well. I would recommend to include a declaration that the study will be done according to the European Law on Data Protection (active since 2018).

Answer: Ethics approval is now presented in the first paragraph of the methods section as well. We also added the date and reference number of the approval letter.
This study was conducted from 2016 till 2018 (before the European Law on Data Protection), therefore we did not include a declaration that the study will be done according to the European Law on Data Protection.

6. Study design (p.4): The study is described as pragmatic observational, which is appropriate but as accurate as it could be. This seems as controlled before-after study, or perhaps more adequately described as a before-after study with a reference group as it is based on self-selection.

Answer: We understand the reviewer’s suggestion, but the study is not what we would call a before-after study, most notably because we included a reference group; the term before-after study is mainly used when no control group is included. After one year of follow-up outcomes are compared between the intervention group and the control group. Primary outcomes are levels of systolic blood pressure and LDL-cholesterol. We mentioned the design in some more detail now in the first paragraph of the methods section.

7. Intervention description (p.5 and further, and table 1): The description seems insufficiently precise to facilitate replication, process evaluation or interpretation of study findings. This comment applies in particular to the activities that deviate from the CVRM guideline, such as the strategies for implementing recommended CVRM. A reporting guideline (e.g. TIDIER) should be used to elaborate the description of interventions. Only from the description of the control/usual care group I understood some of the planned strategies, although the exact differences with usual care remained obscure as the control group would also implement the CVRM guideline. In the description of the interventions, I would also recommend to distinguish between interventions implemented in individual patients, programmatic activities in patient care (e.g. identification and active approach of patients), and the implementation strategies for the implementation of those interventions.

Answer: We apologize that the description of the intervention is insufficiently precise. We appreciate the suggestion to distinguish between interventions in organization of patient care and interventions in individual patients. We applied this suggestion and tried to describe the intervention more clearly on page 7 and further. Also, we added a TIDIER checklist in the appendix.

We realize that the differences between the intervention (integrated care for CVRM) and control (usual care) are somewhat obscure. We appreciate the suggestion to do a process evaluation and will work out this idea.
8. Study procedures (p.11): A case-control study design is introduced only here, but it would be more accurate to present it under study design. The exact procedure for matching needs some further clarification. I suspect that patients from intervention practices will be matched (regarding specific characteristics) with (randomly chosen?) patients from control practices. Will patients in multiple practices (e.g. those who moved houses or shop doctors) be removed?

Answer: We tried to describe the design more clearly now in the first paragraph of the methods section of the revised manuscript to prevent any confusion about our design. This is indeed a matched study, but in our view not a case-control study (where sampling of controls is essential, and that is not the case here). Anyway, we did our very best to describe the more design more clearly in the revised manuscript.

We apologize that the procedure for matching was not totally clear. In the revised manuscript this is described more clearly on page 17. As the actual inclusion of patients is after one year of follow-up, it would not be possible to invite patients who moved houses or shop doctors. Indeed these patients will be ‘removed’. Therefore, we matched 2 control patients to each intervention patient. If the first control patient is not able to/ does not want to participate, the second control patient will be invited (as described on page 17 in the section ‘recruitment of patients for the ZWOT-CASE study’)

9. P.13 The sentence ‘All obtained data (age, gender and risk category) during the identification will be processed anonymously and will not be traceable to individual patients’ is strictly not consistent with current insights anymore. All data can be traced, but I suspect that the authors will create pseudoanonymised data.

Answer: We agree with the reviewer. We corrected this sentence: “All obtained data (age, gender and risk category) during the identification will be processed in a pseudoanonymised manner and the key to the data is not available to the researchers and will be kept within the patients’ general practices.”

10. P.13 I would recommend to use ‘outcome’ rather than ‘endpoint’.

Answer: According to the reviewer’s suggestion, we changed ‘endpoint’ to ‘outcome’.

11. Sample size calculation and statistical analysis (p.14 onwards): Statistical clustering is appropriately taken into account, and it is correct to plan an unconditional (not a matched) analysis. The assumptions for the sample size calculation and its outcomes seem plausible, but I did not actually recalculate it. However, I did not understand these sentences on p.14: ‘’ Both
groups are divided into two groups (patients with CVD and patients with high CV risk) equal in size. The intervention group is selected from 17 general practices and the control group from 9 general practices.’’

Answer: We apologize that the sentence on page 14 was not clear. We changed it into: “The intervention group and control group are both divided into two groups (patients with CVD and patients with high CV risk) equal in size. The intervention group is selected from 17 general practices and the control group from 9 general practices.” (on page 22 of the revised manuscript).

So, for the intervention group 587 patients are selected (divided into two groups of equal size: 294 patients with CVD and 294 patients with high CV risk) from 17 general practices. For the control group 1174 patients are selected (divided into two groups of equal size: 587 patients with CVD and 587 patients with high CV risk) from 9 general practices.

We hope this clarifies this issue.

12. P.15. The number of potential confounders is high for the targeted sample size. What is the strategy for data-analysis to handle chance capitalization and avoid overfitting the regression models?

Answer: We agree with the reviewer that the number of potential confounders is somewhat high. This study is, out of necessity, not randomized. Therefore, correction for potential confounders is important. Since the primary outcome is continuous, with a inclusion target of 740 patients, the potential risk for overfitting is in our view limited (see for example Harrell 2015, p. 72-73). Statistical significance will only be used to evaluate the intervention effect, not to select confounders. We now mention this in the statistical analyses section of the revised manuscript. Additionally, including confounders that may have a clear association with the outcome can actually enhance power (see for example Kahan et al, 2014 or Thompson et al 2015). When reporting the results, we will provide results both uncorrected and corrected for confounders. We will only consider to remove a specific confounder, e.g. COPD, from the analysis when, for example, the number of patients with COPD is very low, (say below 5).

Overfitting may become an issue for some of the dichotomous secondary outcomes. For these outcomes, Firths correction (a shrinkage technique) will be considered.

Discussion

13. As a study of intervention effectiveness, the study design has high risk of bias, because the design is observational and the allocation between study arms is based on self-selection (so motivation and ability to join the program). So, I do not believe that this study can demonstrate
effectiveness as stated on p. 16. Adjustment for potential confounders cannot fully compensate the problems although stated otherwise on p. 16.

Answer: We agree with the reviewer that there is a risk of bias due to the study design. Measures have been taken (notably matching of patients, multivariable analyses) to prevent bias, but we agree that these adjustments may not fully compensate for the risk of bias. We changed some sentences in the first paragraph of ‘strengths’ in the discussion of the revised manuscript to emphasize this. Furthermore, we also refer to our answer to reviewer 1, where we explain why we feel this observational design is a valid approach.

14. The study is done in an existing network of practice, which probably reduces the generalizability of the findings. This limitation is not mentioned, but is substantial as the ambition is to perform a pragmatic study.

Answer: The reviewer raises an important point. We mention this limitation now on page 26. However, we expect that most of the integrated care programmes for CVRM are based on the same Dutch guideline for CVRM and the same international guidelines for CVRM. Therefore, any reduction in generalizability will be limited.

15. A suggestion would be to structure the discussion of study strengths and limitations according to the GRADE criteria, which are now widely used e.g. in Cochrane reviews and by guideline developers.

Answer: We appreciate the suggestion to use GRADE criteria. We support the use of GRADE criteria in reviews and by guideline developers. However, we think that the structure of the discussion for a study protocol is clear enough and therefore did not change it according to the GRADE criteria.