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, Tovah Honor Aronin,

On behalf of my co-authors, I am writing you to resubmit a 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 the journal BMC Family Practice.

We appreciate the interest of the editor and reviewer in our manuscript. We would like to thank the reviewer for his constructive feedback and helpful comments for correction or modification. We believe that the changes clearly improved our manuscript. A point-by-point response to the comments of the reviewer will be appended to this letter. All changes to the manuscript are indicated in the text by using track changes.
We still think that the readership of the BMC Family Practice is the most appropriate audience to which we would like to advocate our study protocol. This paper is highly relevant for general practitioners and researchers in primary care across the world to stay informed about their field 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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Comment: We would like to thank the reviewer for his constructive feedback and helpful comments for correction or modification. We believe that the changes clearly improved our manuscript.

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

1. There are 56 practices but 157 GPs, this must mean that in a practice there is more than one GP.

   Answer: Yes indeed, the practices include solo, duo and group practices.

2. It was not completely clear whether the practices are randomized, or the patients are randomized.

   Answer: We agree with the reviewer on this point. We tried to describe this more clearly now on page 13 and 14 in the ‘Recruitment of patients for the ZWOT-CASE study’ section, where we describe that the intervention is not randomly allocated, but selection of patients is done randomly. To make it more clear earlier in the paper it is now also mentioned in the description of the setting on page 7, where we indicate that practices are not randomized.

3. How was it decided about which practices would start first in the program?

   Answer: We tried to describe this more clearly on page 13 of the revised version. From January 2016, all practices were given the opportunity to participate in the integrated care for CVRM. Every quarter of a year there was a possibility to start with the programme. Participation is not mandatory. GPs have chosen themselves whether they participate in the integrated care or continue with usual care. Practices that have chosen to continue with the usual care did so due to a variety of reasons.

4. Would all practices finally be involved in integrated program?

   Answer: No, participation is not mandatory. In the revised manuscript this is described more clearly on page 13.

5. Why was it not obligatory to have the PNs follow a specialized course in CVRM? By not making it obligatory wouldn't this potentially create an unequal delivery of the service?

   Answer: We agree with the reviewer that this, could lead to inequality in the delivery of the programme. This is the policy of the care group ‘Medrie’. As this study is an observational study we did not have the opportunity to change this policy. However, every PN in both groups followed at least a basic course in CVRM. The specialized course is just an extra training.
Furthermore, as the programme in each practice is based on the same protocol and implemented regionally, we expect the between-cluster variability to be limited.

6. In usual care it was stated that most PNs have had a basic training in CVRM. If that is the case it seems the PNs in usual care may be no different than many of the PNs in the CVRM program?

Answer: We agree with the reviewer that the PNs in both groups probably do not differ. A limitation of the study is that the difference between the intervention group and the control group is not assured, see also the discussion on page 19 and 20 of the revised version. However, the difference between the intervention and control group is not based on the PNs. The difference is that GPs in the control group do not systematically screen their practice population and systematically invite patients for CVRM visits. Furthermore, GPs in the control group do not use the practical guideline for the implementation of integrated care for CVRM, do not register patient data in an information system for integrated care, and yearly benchmark meetings are not mandatory. We therefore expect that there is a difference between both groups.

7. What was the rational for the age range of 40 to 80 years?

Answer: The age of 40 was chosen as the SCORE risk model starts from an age of 40 years. The age of 80 was chosen as we expect that elderly above 70 years who are still vital could benefit from the intervention. This is also the policy of the care group ‘Medrie’.

8. Apparently, the control group risk profile based on complete data on age, sex, smoking status may be missing. What impact will this have on the analysis.

Answer: The incomplete risk profile in the control group will not have impact on the analysis. It might at most affect the selection of patients. However, this is also true for the intervention group as the selection was done in a similar way, based on the same systematically screening of the practice population based on ICPC-coded diagnoses and ATC-codes, and manually checking of medical records. In both groups, it could be that patients whose medical records are missing too much data will not be selected. So the only difference is that in the intervention group the risk profile was completed at baseline, while in the control group this was not possible. This will not affect the analysis at the end of the study.

9. How was the subgroup of patients selected for the study?
Answer: In the intervention group patients are invited by the general practices for an intake consultation between September and December 2016. The general practices randomly invited these patients. After one year of follow-up, these patients will be asked to participate in the study until enough patients are included. Each patient in the intervention group is matched to 2 patients in the control group at the beginning of the study. The selection of these patients in the control group is done randomly. We tried to describe this more clearly on page 14 and 15.

10. Is there an issue with practices choosing to do the intervention versus control? Does this potentially create bias?

Answer: We agree with the reviewer that there is a risk of bias. We also elaborate on this issue in the answer on question 3. As this study is not a randomized study there might be differences between practices in the intervention group and the control group, possibly leading to confounding bias. As described in the discussion on page 19 and 20 this is one of the limitations of this study. However, ample measures have been taken (notably matching of patients, multivariable analyses) to prevent confounding in our study.

11. Why is the actual inclusion of patients after one year of follow up? It seems they should be included at the beginning of the year. This seems confusing to me.

Answer: We understand that this could be confusing. However, the inclusion of patients after one year of follow-up is important to prevent the Hawthorne effect, see also the answer on question 12.

12. To me it is very confusing that the patients are not identified and informed of the study at the beginning. Also, it seems unusual that the GP is not informed until later. There may be concerns about the Hawthorne effect but if both groups are aware of being in a study this should be minimized or at least balanced between the groups.

Answer: We understand the confusion. We expected that the Hawthorne effect would not be equal in both groups. In the intervention group all patients will visit the general practice for an intake consultation. This is part of the intervention. Patients in the control group will not be invited for an intake consultation at baseline. If patients in the control group will be informed about the study at baseline, it could influence for example their lifestyle or stimulate patients to visit their GP for a cardiovascular risk profile. Also, the GP is not informed about which patients are selected for the study, as this could influence the way these patients are treated. In the control group it could even be that the GP has some selected patients not in sight. After one year of follow-up the outcomes will be measured, assuming that baseline characteristics are balanced.
between the groups by matching. Also, we will adjust the analyses for baseline covariates as described on page 18.

13. The authors state the intervention group is selected from 17 GP practices and the controls from 9 GP practices. However, I thought all these practices were involved based on earlier statements by the authors. So, what does this mean? How were the practices selected and how many were selected?

Answer: We understand that this is not totally clear. The source population consists of 56 general practices, of which 37 have chosen to start with the integrated care programme and 19 have chosen to continue to offer usual care. All these 56 general practices were invited to participate in the study. 17 general practices who have started the integrated care and 9 practices who have chosen to continue with the usual care agreed with participation in the study. This is also described on page 13 (‘Recruitment of patients for the ZWOT-CASE study’).