Reviewer’s report

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

Version: 1 Date: 22 May 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

N/A - no experiments or analyses

STATISTICS - Is the use of statistics in the manuscript appropriate?

N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

N/A - no results to interpret
OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS:

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.

Introduction

-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.

-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.

Methods

-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).

-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).
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.

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.

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?

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.

P.13 I would recommend to use 'outcome' rather than 'endpoint'.

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."

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?
Discussion

-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.

-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.

-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.

REQUESTED REVISIONS:

See my earlier review.

ADDITIONAL REQUESTS/SUGGESTIONS:

See my review for suggestions.

Note: This reviewer report can be downloaded - see attached pdf file.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Needs some language corrections before being published

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