Author's response to reviews

Title: A tailored implementation intervention to implement recommendations addressing polypharmacy in multimorbid patients - PomP: study protocol of a cluster-randomized controlled trial

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Author's response to reviews: see over
Reviewer's report:
I read the paper from Jäger et al about the PomP cluster polypharmacy study and I think it is suitable for publication in Trials. I would like to provide some suggestions in order to help the authors think about ways to improve their paper.

- Major Compulsory Revisions
The most challenging methodological characteristic of the PomP study is probably the existence of 3 nested random variables: QC (Center?), GPs (Practice in sample size?); and patient. Please, consider explaining and defining them earlier and refer to them consistently throughout the paper and as separate boxes in Fig 1.
It is true that the three-level-design is a particularity of this study, therefore we have tried to define the different levels already in the introduction in the section about the German health system (p4./5). Figure 1 contains already different boxes for QC and practices. To make this more clear, we have added an explanation of the figure as subtitle. It might be confusing that we use both, primary care practices (PCP) and general practitioners (GP) for the same level. We have now removed “GP” throughout the manuscript and replaced by PCP, whenever it refers to the unit of randomization.

In addition to CONSORT and CONSORT CLUSTER, please consider addressing also the CONSORT extension to non-pharmacologic interventions, which expands on the usual report and analysis of the random patient variable and includes the additional random variables. For example, specifying eligibility criteria for all of them: please, extend the style to explain selection criteria for physicians and patients to QC.
We have added one paragraph for selection criteria of QC (p. 6)

Please, in order to have a clear understanding of the target population, be more precise on specifying the criteria for selecting patients and physicians: Is it all of them? Or only the first consecutive fulfilling criteria and assenting? I.e., In ‘recruitment of patients’, which criteria will the physician follow to select 25?
Actually GPs are free to choose 25 patients from the provided list – all patients on the list fulfill the first 3 eligibility criteria of age, multimedication and multimorbidity. GPs are encouraged to include patients who have from their point of view a high risk for medication problems – however, we do not define this in detail, but leave this to the personal estimation of the physician. We believe that this approach is close to reality, where GPs have to deal with heterogenous patients.

Please, consider also planning to record information both about unselected units (at each level) and characteristics of higher level units in order to describe them at baseline accurately —as initial patient characteristics are usually described.
Indeed, we have planned to collect this data in the context of a comprehensive process evaluation, which is prescribed in a separate protocol. We have added this on page 9.
Although provided ICCs specify higher variability among physicians than among centers, please consider addressing, for example in your discussion, if selecting just 4 centers may compromise representativeness of results: How many centers are there in the studied health area?

Indeed, the number of QC is low and does not aim at representativeness. We randomize on QC level to avoid contamination by randomizing GPs who meet regularly in the same QC into the intervention and control group. Furthermore, this study has a pilot character. If the intervention is successful, it could be offered to more QC in Germany. We have added the number of QC in the German federal state “Baden-Wuerttemberg” (p. 5) and pointed to the non-representativeness of the number of QC included in this study (p. 13).

**Minor Essential Revisions**

Please consider including a concrete reference to the formula of sample size or its concrete application (calculation).

Please, in accordance with CONSORT, consider being more precise about the randomization, allocation concealment, and the evaluator blinding processes.

This study protocol follows the CONSORT criteria, which state the following for the randomization section:

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>8a Method used to generate the random allocation sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>8b Type of randomisation; details of any restriction (such as blocking and block size)</td>
</tr>
<tr>
<td>Allocation</td>
<td>9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
</tr>
<tr>
<td>Concealment</td>
<td>10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
</tr>
<tr>
<td>Implementation</td>
<td>11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
</tr>
</tbody>
</table>

Reading the study protocol carefully, we could not identify which information is missing. It would be very kind if you could be more precise on which information should be added to the manuscript.

Please, consider addressing, for example in the discussion, the risks due to the open nature of the trial, i.e., performance bias due to additional ‘interventions’ in one of the arms or rater bias due to evaluators guessing the center arm.

It is true that due to the lacking blinding there is a risk of performance bias in this study. However, the pragmatic character of the trial, which does not allow blinding, implies also a high external validity. We consider this a strength of this study and have included this into the discussion section on p. 13.

And, in combination with the cluster design, selective selection of centers, physicians or patients: would any of them be able to decline after knowing the allocated center?

All participants are able to decline at any time of the study. Allocation will be concealed until baseline data collection is finished in each center. We have specified this on p. 11.

Please consider giving more relevance to confidence intervals.

We have specified this on p. 10

Please consider specifying that a fully specified statistical analysis plan will be written previous to the results in order to avoid ambiguities (for example, the way of adjusting for baseline, transformations to main outcome for improving distributional assumptions, and so on).

We have specified this on p. 10
**Discretionary Revisions**

Please consider specifying the main analysis closer to ‘main outcome’ and ‘Sample Size’.

*We have moved the section “Statistical methods”, it follows now the section “Sample Size”.*

Please, consider trying to improve your editing (i.e., primary outcome is specified twice in the abstract methods’ section; or the second line of ‘health system’ specifies ‘...as has...’.

*Thank you for this hint, we have once again carefully read and corrected the manuscript focusing on editing and language issues.*

My best wishes for the next phases of your meritorious work.

**Erik Cobo**

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests