**Author’s response to reviews**

**Title:** Impact of training and structured medication review on medication appropriateness and patient-related outcomes in nursing homes: results from the interventional study InTherAKT

**Authors:**

Angelika Mahlknecht (angelika.mahlknecht@pmu.ac.at)

Laura Krisch (laura.krisch@pmu.ac.at)

Nadja Nestler (nadja.nestler@pmu.ac.at)

Ulrike Bauer (ulrike.bauer@pmu.ac.at)

Nina Letz (nina.letz@pmu.ac.at)

Daniel Zenz (zenz@smart-q.de)

Jochen Schuler (jochen.schuler@pmu.ac.at)

Laura Fährmann (laura.faehrmann@uni-muenster.de)

Georg Hempel (georg.hempel@uni-muenster.de)

Maria Flamm (maria.flamm@pmu.ac.at)

Jürgen Osterbrink (juergen.osterbrink@pmu.ac.at)

**Version:** 3 **Date:** 14 Aug 2019

**Author’s response to reviews:**

Dear Editors,

Thank you again for the possibility to revise our paper “Impact of training and structured medication review on medication appropriateness and patient-related outcomes in nursing homes: results from the interventional study InTherAKT” (BGTC-D-18-00563R2).

We thank you for your editorial comments. We responded to all comments on a point by point basis and changed our manuscript where appropriate. Our answers are directly typed into the reviewers' comments and marked by "XXX".
Changes to the manuscript are indicated in the text by highlighting:

Revision 1: yellow marking,
Revision 2: grey marking,
Current revision: blue marking.

We are looking forward to receiving your response.

Sincerely,
Dr. Angelika Mahlknecht

Institute of General Practice, Family Medicine and Preventive Medicine
Paracelsus Medical University, Strubergasse 21, 5020 Salzburg (Austria)

Editorial Comments
Thank you for your revised submission to BMC Geriatrics. Before we can accept your manuscript, please address the following editorial points:

1. The two different raters evaluated at different times. Thus, it may be hard to tell whether the change of MAI from t0 to t2 is due to intervention or different raters, based on available data. As the authors responded, checking IRR on a subsample of patients by retrospective additional rating might not be reliable too. Therefore, this limitation needs more discussion in article.

XXX Response to Editors: Thank you for this indication. We amended the statement in this regard in the Discussion section to point this out more clearly (line 481-487). To the Methods section, a paragraph in this regard had yet been added (line 225-229) during the first review process. XXX
2. Table 3: Did the authors consider adjusting for baseline characteristics (eg, using linear mixed models)?

XXX Response to Editors: Thank you for your question. We did not consider the use of a mixed model to adjust for baseline characteristics in our study. As our study design did not include a control group (we report this as the main limitation in the Limitations section of the manuscript) changes in the measured outcomes are not directly assignable to the intervention. Therefore also the intervention itself could not be incorporated as a predictor in a multiple regression model together with other baseline characteristics.

Other baseline characteristics could be incorporated in a multiple regression model to investigate to which extent the variation in the baseline MAI-Sumscore is explained by a model that contains certain variables being associated with inappropriate medication. E.g., a systematic review by Nothelle et al. (2017) summarises determinants for potentially inappropriate medication use in adults ≥ 60 years in nursing homes: age, gender, number of medications, cognitive impairment, etc. In our manuscript, we have depicted the relationship between MAI-Sum and MAI-change by reporting the correlation coefficient in Tab.3.

However, the main focus of interest in our study was the change of MAI-Sum, not the MAI-Sum at baseline. As the number of drugs is already part of the MAI-Sum and therefore strongly correlated with it (r= 0.7) it should not be included in a regression model. And even if we knew how much variance is explained by a model using certain baseline characteristics we could not draw conclusions regarding the effect of our intervention or how much more variance would be explained in a model where it is incorporated.

To substantiate the relationship between MAI-Sum at baseline and MAI-change we conducted a linear regression analysis for the sample with n=81 (sample with exclusion of two outliers, see legend of Tab.3) with the baseline MAI-Sum as predictor and the MAI-change as response variable. The MAI-Sum at baseline explains 32.8% of the variance of the MAI change. We included this information in Tab.3 and added it to the Results section of the manuscript (line 324). XXX

Linear regression to predict the MAI change (n=81)

Table (please see attached cover letter to view the formatted table)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAI-Sum at t0</td>
<td>-.50*</td>
<td>.08*</td>
<td>-.57**</td>
<td>.33**</td>
</tr>
</tbody>
</table>

Legend: * p<0.05, ** p<0.01
MAI-Sum Weighted MAI sum-score

Literature cited in this response:


3. It seems that the study excluded all drop-out, even partial data is available. Did the authors inspect the missing mechanism of the data (MCAR, MAR, MNAR)? Also, it might help by comparing baseline characteristics between two groups of drop-out and remained subjects, and performing some sensitivity analyses to evaluate the robustness of the results to missing data.

XXX Response to Editors: Thank you for this comment. As we focused on the change of the primary endpoint (MAI) between t0 and t2 and therefore on the process, we included in the analysis every nursing home resident (NHR) from whom we could collect data at all times of measurement. Reasons for missing data were well documented. The drop-outs between t0 and t2 were mostly due to death (26 of 120 NHRs = 21.7%). Death usually does not lead to a systematic error; therefore, robustness of the results to missing data is assumed. When planning the study we expected a drop-out rate due to death of approximately 27% per year due to the mortality rate of our investigated population. As the drop-out rate is not specifically higher or lower than expected we assume that our remaining sample is a randomly taken sample of our baseline-sample and we classify the mechanism as MCAR.

Other reasons for drop-out were: change of the general practitioner by NHRs, withdrawal of the pharmacy, severe terminal illness of NHRs, leaving the nursing home by NHRs and change regarding the responsibility for the supply with medications.

These drop-out reasons were not directly linked to the dependent variable in our sample (MAI-Sum). However, as a large body of literature has shown medication inappropriateness to be in line with increased frequency of adverse drug events leading to higher numbers of hospitalisations or even increased mortality rates, one could assume a relationship between these reasons for drop-out and medication appropriateness. Thus, as suggested, we also compared the baseline characteristics between the NHRs who remained in the study sample and those who dropped out. As expected we found no difference between the drop-outs and the remaining subjects concerning MAI-Sum (Tdf=118=0.83, p= 0.409) or MAI-Mean (Tdf=118=0.98, p= 0.329). We included this information in the Results section of the manuscript (line 298-299).

XXX