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

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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-18-00563R1).

We thank both reviewers for their comments and suggestions. 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).

We are looking forward to receiving your response.

Sincerely,

Dr. Angelika Mahlknecht,
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Reviewer 1
1) There are some minor issues with the English expression e.g. Abstract line 55-unbound and consistent access. This would be better phrased as 'unlimited and consistent access…'

   XXX Response to Reviewers/Editor: Thank you for this suggestion. We amended this term in the abstract. XXX

2) Another example is (line 77) '…a need of improved interprofessional communication is pointed out'. Better phrased as '…a need for improved interprofessional communication is highlighted'.

   XXX Response to Reviewers/Editor: Thank you for this indication. We changed this sentence according to your suggestion. XXX

3) There are other examples were the English expression is not quite right. The authors have explained in their response what was meant by quarantine, but this also needs to be explained in the text (line 142).

   XXX Response to Reviewers/Editor: We added a short explanation to line 142 (“isolation due to infectious diseases”). XXX
4) Line 155-what is meant by particularity of drug therapy?

XXX Response to Reviewers/Editor: This refers to the special features and challenges of drug therapy in older adults. We amended this sentence to “drug therapy in older and multimorbid adults” (line 155 – 156). XXX

5) And line 158-prioritizing?

XXX Response to Reviewers/Editor: We added an explanation in this regard (line 158 – 160). XXX

6) Line 185-what is meant by conciliated?

XXX Response to Reviewers/Editor: We amended this term to “complete” (line 187). XXX

7) Line 223-rating pharmacists? This term is not clear. Do the authors mean those pharmacists who conducted the MAI ratings? If so, this should be described in this way.

XXX Response to Reviewers/Editor: Thank you for this question. We added “who conducted the MAI ratings” to clarify this (line 226 – 227). XXX

8) Line 256-what is meant by 'control variables’?

XXX Response to Reviewers/Editor: The control variables were not outcomes, but they were collected to describe the intervention periods. The term “control” is indeed misleading, we therefore amended it to “variables describing the intervention period” (line 258). XXX

9) Line 262-rather than 'descriptive character', this should be described as 'descriptive nature'

XXX Response to Reviewers/Editor: Thank you for this indication. We amended this term according to your suggestion (line 266). XXX
10) Line 281-when the authors state that 'footage of this event' was provided, does this mean that the training event was recorded?

XXX Response to Reviewers/Editor: Thank you for your query. The first onsite training was recorded in order to provide access to the contents also to those study participants who were not able to attend this event. We added a statement in this regard (line 299 - 300). XXX

11) Line 353. The authors attribute some of the effects seen to the educational effects of training. How can they be sure about this?

XXX Response to Reviewers/Editor: Thank you for this indication. We agree that this is a hypothesis rather than a sure affirmation. We amended this sentence to “This could be related to potential educational effects of the training” (line 404). XXX

12) Line 367-this does not make sense in English-'.. remained unvaried high’?

XXX Response to Reviewers/Editor: We amended this expression to “mean number of drugs was high and did not change substantially” (line 422-423). XXX

13) In Figure 2, typo 'performe'. There is no 'e'. it should be 'perform'

XXX Response to Reviewers/Editor: Thank you for this indication. We corrected this in Fig2. XXX

Reviewer 2

1) The authors have addressed most comments adequately. The length of the text (and tables) has somewhat increased, and there may have been missed opportunities to condense the information presented. If needed, it seems possible to cut down some of the information presented. For example in table 4, you could provide only data from the 83 (or 81) sample, and skip the distinction between the groups with MAI sum above or below 24); a summary of the information not presented in the table can be provided in one sentence.

XXX Response to Reviewers/Editor: Thank you for this helpful suggestion. We amended Tab.4 according to your suggestion and provided additional information in the text (line 324 – 327). XXX
2) Coming back to MAI ratings (primary outcome measure). I am surprised that the "drug-disease" interaction rates so low. In older people, it very frequent and much more common than for DDIs to have a clinically significant drug-disease interaction; eg a patient with a fall and taking a BZD. Can you please comment?

XXX Response to Reviewers/Editor: Thank you for this indication. We performed a non-systematic literature search in this regard (the literature is listed on the bottom of this paragraph) and found a variety of reported frequencies of drug-disease interactions (12.2%-51.9%).

Older age, multiple prescriptions, former hospitalization and comorbidity were identified as factors associated (Onder 2018, Aspinall 2015, Lindblad 2005) (complete citations see below).


A recent study conducted by Hanlon et al. (2017) found a prevalence of 25.1% for drug-drug interactions, but a lower prevalence of 16.0% of drug-disease interactions in community-dwelling older adults.

There is consensus that data on important clinical outcomes from drug-drug and drug-disease interactions are limited (Gnjidic 2013, Lindblad 2005, Hanlon 2017).

In our study, the prevalence of drug-disease interactions was rated within the MAI and it was not a direct subject of investigation, thus, we cannot compare our results to the prevalences of the cited studies.

The pharmacists who performed the MAI ratings valued the drug-disease interactions according to the medication lists, documented diagnoses, laboratory parameters and documented events e.g. falls or hospitalizations. They had no access to the online platform to consider additional parameters as the online platform was accessible only to the healthcare professionals who conducted the therapy check.

In the case of falls, which represent a risk condition for drug disease interactions, documentation in our study sample was inconsistent throughout the study period (see also Tab.2, line 292). This may have contributed to the low drug-disease rating in our sample. We added a statement in this regard to the Discussion section (line 407 – 409). XXX

Moreover, some evidence suggests that explicit criteria (e.g. Beers criteria) may be more efficient in detecting drug-disease interactions than implicit criteria (Lindblad 2005).

Literature cited in this response:


3) Unless this has changed, the instructions of the MAI mention that when the rating on "indication" is inappropriate, then the rating for criteria 2, 3, 4, 5, 9 and 10 must also be inappropriate. Why was this not applied in the current study?

XXX Response to Reviewers/Editor: Before the beginning of the study, the pharmacists performing the MAI ratings contacted Prof. Joseph T. Hanlon to receive detailed information regarding the use of the MAI. Prof. Hanlon provided instructions which were last updated on 2014 Nov 01. In these instructions, it is stated that if item 1 (indication) is scored C (inappropriate) also the criteria 9 and 10 are scored C. The items 2, 3, 4 and 5 are not mentioned to be rated as inappropriate as well in this context.

In our opinion, it seems plausible to rate these items independently from indication: e.g. a drug which is scored “inappropriate” according to the MAI in some cases might be prescribed intentionally if the expected benefit outweighs the risk. In this case, the items dosage and direction can be appropriate even though the indication is rated as inappropriate.

The used MAI instructions are attached to this submission as additional file. We added a statement concerning the applied MAI instructions to the Methods section (line 228 – 229). XXX

4) The fact that the pharmacist evaluating at t0 is not the same pharmacist who evaluated at t1-2 remains a problem. It is good that a limitation on this aspect has been added, however the authors should have checked IRR on a subsample of patients (eg minimum 10-15 patients).
XXX Response to Reviewers/Editor: Thank you for this indication. At every time of measurement, one clinical pharmacist conducted the MAI rating (one pharmacist at t0 and another pharmacist at t1/t2). They received the same extensive instruction and supervision by one adept clinical pharmacist throughout the study period.

To our knowledge, from a statistical point of view, a calculation of Inter-Rater-Reliability is not possible neither

(a) within one time of measurement, because only one person conducted the ratings at every time of measurement, nor

(b) between the different times of measurement, because the effect of the intervention lies between the different testing times and affects the results. Thus, differences in MAI rating between testing times could not be distinguished between rating differences or differences due to the intervention. Nevertheless, both raters were supervised by the same clinical pharmacist who checked subsamples of all ratings before forwarding the results to the statistical experts who analysed the data.

The person who conducted the MAI ratings at t0 is not available any more. The rater who performed the MAI ratings at t1 and t2 is still available, however, we do not consider a retrospective additional rating of a subsample of patients by this rater as reliable, because she meanwhile has gained additional experience in MAI ratings and the present rating results may not be fully comparable to the former results of 2016/2017.

If the reviewer knows a possible way to calculate the IRR under these circumstances we kindly ask to inform us; in this case, we would calculate the IRR and report it in the manuscript. XXX

5) In line with this, the observation that criterion "indication" significantly improved over time, but that there was no significant modification in the number of drugs taken raises question. The first hypothesis is that indication really improved, and that overused medications were deprescribed, but that this was counterbalanced by adding underused medications. The second hypothesis is that the significant difference in indication ratings over time comes from differences in the evaluation performed by the two pharmacists. This could be explored by looking at the classes of medications prescribed at t0, t1 and t2; and at deprescribing and new prescribing events. Could the authors consider this option?

XXX Response to Reviewers/Editor: Thank you for these considerations. We conducted a spot check analysis of ten patients in this regard and examined the number of medications as well as the item indication at all times of measurement; moreover, we compared the medication lists of these patients at t0, t1 and t2 to retrieve deprescriptions and new prescriptions. The results show that:
- In all investigated cases, medication regimens changed throughout the study period: overall, 45 new prescriptions were added and 32 of these (71%) were rated as appropriate regarding indication (scored 0 in the weighted scoring); 43 drugs were deprescribed, in 34 of these cases (79%) indication was rated as appropriate.

- In five of the investigated patients, the item indication improved over time while the number of prescriptions did not change substantially except one case which showed a remarkable increase of medications (from one drug at t0 to five drugs at t2).

- In one of the investigated cases, indication was rated as fully appropriated at all times of measurement while the number of drugs decreased slightly.

- In the remaining four cases, the item indication remained at the same level or worsened slightly while the number of drugs did not change substantially.

According to this spot check analysis, whose validity is of course limited as it is not representative for the whole study sample, real improvements in indication by deprescribing of inappropriate medications and adding of underused drugs seem not to have played a role. In our opinion, the improvements of the criterion indication are most probably due to the mentioned improvements in documentation of diagnoses which were achieved by the intervention: it was part of the study’s purpose to create a central documentation tool and thus to enhance completeness of documentation and of the patients’ information provided to the healthcare professionals concerned. We added a statement to the Discussion section to point this out more clearly (line 405 – 406).

A complete analysis of the whole study sample to further investigate this question was not possible within the requested timeline as this would have required a manual check and comparison of 83 medication data files per three times of measurement.

As we were not able to conduct an IRR analysis (see response to comment 4), we cannot totally exclude that the results are affected by inter-rater differences. We added a statement to the Discussion section (Limitations) in this regard (line 480 – 481). XXX

6) We really miss a table describing ATC classes (ATC level 3, or minimum level 2) mainly used at different time points here (sorry for not mentioning this at the first review); this would be most helpful, and would help to better understand what happened.

XXX Response to Reviewers/Editor: Thank you for this comment. We provided a table depicting the weighted MAI sum-score for the mainly used ATC classes level 2 (see Results section, new Tab.5, line 367). Furthermore, we added an explanation to the Results section (line 330 – 341) and a statement to the Discussion section (line 426 – 429) in this regard. XXX