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 for 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-18-00563).

We thank both reviewers for their helpful 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.
We are looking forward to receiving your response.

Sincerely,

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Reviewer 1

1) Thank you for the opportunity to review this paper. I have a number of comments, which largely relate to the methodology. This reads more like a proof of principle paper. Do the authors consider this as a pilot?

XXX Response to Reviewers/Editor: Thank you for your query. This study can be considered as a pilot because the online platform was newly designed and tested within this project, and some functions were revised during application according to the suggestions of the study participants.

The process applied in this study has subsequently been adapted, implemented within primary documentation and used within a non-randomized controlled trial conducted in Austria between 2016 and 2018. Results of the Austrian study are being analyzed and processed for publication (published study protocol: Schaffler-Schaden D, Pitzer S, Schreier M, Dellinger J, Brandauer-Stickler B, Lainer M, Flamm M, Osterbrink J. Improving medication appropriateness in nursing home residents by enhancing interprofessional cooperation: A study protocol. J Interprof Care. 2018 Jul;32(4):517-520). XXX
2) They are explicit that it is not a randomised study (single arm intervention), and therefore, the conclusions that can be drawn from this are somewhat limited. There is another study which was conducted in the USA which focused on interprofessional communication between prescribers and pharmacists—see LAPANE KL, HUGHES CM, CHRISTIAN JB, DAIELLO LA, CAMERON KA, FEINBERG J. Evaluation of the Fleetwood model of long-term care pharmacy. Journal of the American Medical Directors Association 2011; 12: 255-363 and LAPANE KL, HUGHES CM, DAIELLO LA, CAMERON KA, FEINBERG J. Impact of information technology in the medication monitoring phase to prevent adverse drug events in nursing homes. Journal of the American Geriatrics Society 2011; 59: 1238-1245

XXX Response to Reviewers/Editor: Thank you for these interesting references. We reviewed the mentioned articles and cited them in the text (line 80-84 and line 97-101). XXX

3) I was not sure what was meant by isolation in respect of exclusion criteria for residents.

XXX Response to Reviewers/Editor: Isolation of residents referred to quarantine due to infections; this was an exclusion criterion because of the lack of possibility to perform the tests for the patient-related secondary outcomes with these persons. In these cases, only the medication appropriateness, the number of drugs and drug-drug interactions could have been studied and we would not have been able to assess changes in health-related outcomes. We amended “isolation” to “quarantine” in the manuscript (line 142). XXX

4) The estimated sample size of 300, but this was not achieved and was not commented on in the Discussion. And I think this also affects the data which are shown in Figure 4.

XXX Response to Reviewers/Editor: Thank you for raising this important issue. By means of the power analysis we calculated a necessary sample size of 58 NHRs sufficient to prove significant changes in the primary outcome MAI. This sample size was achieved in our study with 83 NHRs rendering it unnecessary to be mentioned in the Discussion.

The reported number of 300 NHRs is the suggested number of residents needing to be contacted for participation in order to finally achieve the necessary sample size of 58 NHRs. This number of 300 NHRs included possible drop-outs due to death, withdrawal of participation, etc. and was based on previous study experiences in NHs of the research group. We contacted two statistical experts who recommended only reporting the necessary sample size (58 NHRs) in the manuscript; they considered it unusual to also publish the number of persons who should be contacted in order to achieve the aspired and necessary sample size.

As the sentence in the former line 128-129 was also misleading because it combined two different aspects of our sample-planning process (1. the number of NHRs who should be
contacted to finally achieve the necessary sample size, 2. a possible subgroup analysis for which we did not calculate sample sizes a priori), we deleted this misleading sentence and amended it to “According to comparable trials [28], an effect size of at least dCohen=0.33 was assumed, leading to a necessary sample size of 58 NHRs for the primary endpoint.” (line 145-147).

5) How did the authors decide on the content of intervention?

XXX Response to Reviewers/Editor: Thank you for this important question. The training concept and the therapy check process were developed by the multi-professional project team of nurses, GPs, clinical pharmacists and a specialist in internal medicine with expertise in polypharmacy, who together integrated current evidence, expertise and collective experiences regarding geriatric pharmacotherapy, challenges in inter-professional collaboration and e-learning. A statement to clarify this has been added to the Methods section (line 149-152); additionally, we listed the topics covered by the interprofessional training (line 155-159).


6) A diagram showing the different stages of the therapy check process would be very useful as I could not quite follow the various steps.

XXX Response to Reviewers/Editor: Thank you for this helpful suggestion. We added a graphic showing the different steps of the therapy check process (new Fig.2 with reference in line 182) to depict the different stages more clearly.

7) It would also be helpful to know where pharmacists and GPs work in relation to nursing homes in Germany. Are they based in nursing homes or are they in clinics/offices/community pharmacies?

XXX Response to Reviewers/Editor: Thank you for inquiring about this detail. In Germany, GPs work usually in single-handed or group GP offices which are not situated within the NH. If a patient is admitted to a NH, he/she usually keeps his/her former GP.

Pharmacists supplying NHs are also usually not based in nursing homes, but employed in community pharmacies. Pharmaceutical care, education and delivery of medication are regulated by contracts between the NH and the pharmacy. Pharmacists are not obliged to visit NH at
definite points in time, but visits are conducted for control of medication storage and use; e.g. every six months. We added information in this regard to the Background section, line 67-73. XXX

8) I was also very unclear why study assistants would enter data as part of the therapy check process.

XXX Response to Reviewers/Editor: The role of the study assistants was to support the nurses regarding the use of the online platform (data entry and performance of the therapy check steps). This was not planned a priori, but became necessary due to the additional documentation workload induced by the study, as the online platform could not be connected to the primary documentation systems of the NHs. Processes conducted by the study assistants were always performed under prior consultation and agreement with the nurses.

We added a reference “see below” to the first statement in this regard in the manuscript in line 183, as in line 210-217 the reasons for involving study assistants are explained (“Documentation in the I-oP had to be conducted in addition to routine documentation in the respective electronic health records as the tool has not yet been embedded into primary documentation. Thus, study assistants were recruited to help nurses with data entry and to support the therapy check in the NHs in close collaboration with the nurses.”). The involvement of study assistants is also discussed in the Limitations section (line 407-411). XXX

9) How did the GP communicate with residents (see line 163)?

XXX Response to Reviewers/Editor: The GPs communicated with their respectively treated residents or their legal representatives directly i.e. during NH visits. We added this information to the Methods section, line 192. XXX

10) I could not really follow the description of the results section which described the intervention. I think this is why a diagram in the Method might help to explain how the system should have worked, and then perhaps another diagram showing what happened.

XXX Response to Reviewers/Editor: Thank you for this indication. As stated in the Methods section in line 218-220, the therapy check was intended to be completed at least once until t1 for every resident. We added a reference to the above-mentioned new Fig.2 also to the Results section (line 289) to explain more clearly the steps which were actually completed until t1. XXX
11) I found the Discussion was quite fragmented and did not flow very well. It would be helpful to have a native English speaker comment on this paper.

XXX Response to Reviewers/Editor: Thank you for this suggestion. We amended, shortened and rephrased parts of the Discussion section (see yellow markings) and forwarded the paper again to a native English speaking person for proofreading. XXX

12) As stated previously, there is nothing about under-recruitment.

XXX Response to Reviewers/Editor: Actually, the estimated necessary sample size of at least 58 NHRs was achieved as 83 NHRs could be included at each time of measurement. Thus, under-recruitment is not given. This was formulated in a misleading way in the Recruitment section (see above, response to comment no. 4). XXX

13) Do the authors plan to undertake a randomised study?

XXX Response to Reviewers/Editor: The use of the InTherAKT online platform is currently being planned for extension into German nursing homes. In course of this follow-up project, a RCT is intended to be conducted in Germany.

As stated above, a non-randomized, controlled trial adapting and implementing the methods used in our study has already been conducted in Austria. Results have yet to be published. XXX

Reviewer 2

The paper describes the effect of an intervention combining education of HCPs in NHs with medication review and information sharing through HIT on appropriateness of prescribing. The paper is well written, this study adds to the current body of literature on this topic. The main weakness lies in the uncontrolled study design. This is acknowledged in the limitations and conclusion as well.

XXX Response to Reviewers/Editor: Thank you for the encouraging feedback. XXX
Main comments

1) The primary outcome measure is appropriateness measured with the MAI. MAI scores at patient and drug level are presented. However, it would be valuable to present additional data on MAI findings, to better understand what lies behind the significant improvements in overall scores. So at minimum, a table with overall ratings for each of the 10 items would be useful. If possible, overall data per ATC level 1 would also be of added value.

XXX Response to Reviewers/Editor: Thank you for pointing out these interesting issues. In response, we provided a table listing overall scores for each MAI item and added a short explanation (Tab.4, Results section, line 305-311 and line 317; Discussion section, line 352-354).

An analysis regarding different drug classes was not a priori planned (except for analgesics where we included the ATC codes M01, N02A and N02B). We did some spot checks and found that only a few different drug classes from ATC level 1 were well represented among our sample. Therefore, an analysis at this level would not result in valuable additional information. Furthermore, data from the current study are not available such that they can be analyzed for this question. Nevertheless, this is an interesting indication which we will consider a priori for the German follow-up project (see above, last comment of Reviewer 1). XXX

2) Data on the validity/reliability of MAI measurements should be provided. It is mentioned that several clinical pharmacists were involved. What was their level of training/experience? Which data did they use for their evaluation? Were they blinded with regard to the time information (i.e. did they know what was t0, t1 or t2 data (in that case, knowing that the study was uncontrolled, they might have been biased towards more favorable evaluation for t1/t2 as compared to t0)? Was reliability between raters evaluated?

XXX Response to Reviewers/Editor: At every time of measurement, one clinical pharmacist conducted the MAI rating. Two different clinical pharmacists were involved throughout the study period: one at t0 and the other one at t1/t2. They worked for the first time with the MAI, but received the same extensive instruction and supervision by one adept clinical pharmacist throughout the study period. We added a statement in this regard to the Methods section, line 223-225.

The rating pharmacists used data collected by the project team from the NH documentation. We added more details concerning the collected data to the Methods section, line 225-230; see also published study protocol: Mahlknecht A, Nestler N, Bauer U, Schüßler N, Schuler J, Scharer S, Becker R, Waltering I, Hempel G, Schwalbe O, Flamm M, Osterbrink J. Effect of training and structured medication review on medication appropriateness in nursing home residents and on

Due to logistical restrictions, information regarding time of measurement could not be veiled; therefore, the clinical pharmacists were aware of the different times of measurement and a bias towards a more favorable evaluation at the end of the study cannot be excluded. The patient IDs were blinded to the pharmacists throughout all times of measurement. We added a statement in this regard to the Discussion section, line 418-421.

As only one rater per time of measurement was involved, intra- and inter-rater reliability of this study could not be calculated due to the effect of the intervention which lay between the different testing times and affected the results.

In general, as described in a narrative review, the MAI has acceptable inter- and intra-rater reliability (Hanlon JT, Schmader KE. The medication appropriateness index at 20: where it started, where it has been, and where it may be going. Drugs Aging. 2013 Nov;30(11):893-900).

XXX

3) Please clarify further the medication review process that was part of the intervention (l158-168): did the GP do a medication review? If so, what level? I suppose they did some form of medication review, because I assume that the medication review level 1 done by the pharmacist is not sufficient enough, as it focused on a limited number of aspects of appropriateness. Please also clarify what support did the HCP have to conduct the medication review (in addition to the training provided at the beginning of the trial).

XXX Response to Reviewers/Editor: Thank you for this important question. The GPs were instructed to (1) check the medication plan received from the nurses and to complete it where appropriate, and (2) to perform a comprehensive medical review of the drug regimens based on updated medication/patient information (clinical and laboratory parameters) and on knowledge gained during the training. This medical review was not defined according to a specific level but can be equalized to an advanced medication review according to the Pharmaceutical Care Network Europe Guidelines (http://www.pcne.org/upload/files/91_Messerli_2015.pdf).

GPs had also the possibility to ask the pharmacists specific questions relating to the medication. We added this information in the Methods section, line 184-188.

HCPs were supported during the whole intervention phase by the project team regarding technical queries arising from the use of the online platform and by timeline reminders (see Methods section, line 213-217). XXX
Other comments

Background

4) First paragraph: authors mention issues of communication between GPs and specialist physicians. It is therefore unclear that interprofessional communication, as used in the rest of the paper, is also referring to communication between GPs, nurses and pharmacists.

XXX Response to Reviewers/Editor: Thank you for this comment. Since a number of different prescribers is often involved, the exchange of information regarding medication becomes crucial. This regards not only physicians, but all HCPs involved in the various steps of the medication process. We corrected the respective sentence (line 74-75) to point this out more clearly. XXX

5) L74: the Come-on study is also using HIT to facilitate information sharing and communication between HCPs in nursing homes (see protocol paper by Anrys et al)

XXX Response to Reviewers/Editor: Thank you for suggesting this interesting article. The COME-ON study uses HIT in three ways: within the educational part of the intervention as an e-learning platform, during case conferences for recording drug-related problems and as a web application which allows sharing patient-related information between HCPs and generating reports of case conferences. It is this third function which has similar characteristics to the InTherAKT online platform. However, it is not used to the same extent for communication pathways as it is in our study where all steps of the multi-professional therapy check were performed within the online platform; in addition, messages were generated and sent by the same tool. Nevertheless, the indication of the COME-ON study provided useful information and a citation was added to the manuscript (line 84-87). XXX

Methods

6) As the medication use process in NHs can substantially vary between countries, some background information on this would be useful (e.g. number of GPs, restrictions or guiding for prescribing, role of nurses, pharmacist,…)

XXX Response to Reviewers/Editor: Thank you for this consideration. In Germany, regular review and adjustment of medication in NHs is not common. GPs usually visit their patients living in nursing homes regularly, but the frequency of visits often varies. Patients are also visited and prescribed drugs by different specialists. The number of GPs attending one nursing home is variable, usually there is not one single GP per NH, but several different GPs. This regards also pharmacists supplying NHs. Pharmacists are legally obliged to ensure adequate provision and storage of drugs and medical products. Additionally, they perform analyses of
drug-drug interactions. They are, however, not consulted on a regular basis for medication reviews. Nurses deliver medications and monitor the residents’ clinical condition. We provided this background information in our published study protocol and added a paragraph with reference to the study protocol to the Background section (line 67-73). XXX

7) L117: what does "intensified treatment" refer to?
XXX Response to Reviewers/Editor: This refers to a special contract of care, where GPs commit themselves to visit their patients living in NHs periodically and with determined frequency; additionally, GPs holding these contracts collaborate with a special care assistant nurse, who meets patients regularly and refers any news and problems to the respective GP. We explained this in the study protocol and added a respective reference to the manuscript (line 136). XXX

8) L123: why was isolation an exclusion criterion?
XXX Response to Reviewers/Editor: We amended “isolation” to “quarantine” in the manuscript (section Recruitment and sample size, line 142). This was an exclusion criterion because of the lack of possibility to perform the tests for the patient-related secondary outcomes with those residents. In these cases, only the medication appropriateness and the number of drugs and drug-drug interactions could have been studied and we would not have been able to assess changes in health-related outcomes. XXX

9) L140: 'therapy check process': what is the difference between this term and the term structured medication review that is used in the title and at other places in the manuscript? Please clarify
XXX Response to Reviewers/Editor: Thank you for this question. The two terms actually describe the same procedure.

“Structured medication review” was used as an “umbrella term” in the title, the abstract and the study hypothesis to summarize in a generally intelligible way what was done within this part of the intervention.

“Therapy check process” is the technical term which we created as the proper name for the procedure conducted by means of the online platform; it consisted of the defined communication steps and the medication review performed by GP and pharmacist (see also current Fig.2, which has been added to the manuscript according to suggestion of Reviewer 1). XXX
Results

10) Table 4. P-DDIs: how were these evaluated? I suppose it is not from the MAI, as the MAI aims to identify actual (and not potential) DDIs. Also, it would be more meaningful to present this data as % of NHRs with at least 1 pDDI

XXX Response to Reviewers/Editor: Thank you for this indication. The clinical pharmacists rated the clinical significance of a DDI for each patient individually by using the UpToDate/Lexicomp database (see reference in Table 1). They evaluated actual DDIs as stated in item 6 of the MAI. We deleted “potential” in the table (current Tab.5, line 332) and throughout the manuscript as it was misleading in this context.

In Tab.5, the percentage of NHRs with at least one severe DDI is given; we amended “% NHRs with severe DDIs” to “% NHRs with ≥ 1 severe DDIs” to point this out more clearly. XXX

Discussion

11) L327-329: one possibility to check for this would be to discuss the results of the MAI criterion relative to indication (item 1) and duration (item 9). There might have been missed opportunities to deprescribing for different reasons (HCPs not identifying overtreatment, low perceived self-efficacy to deprescribe,…)

XXX Response to Reviewers/Editor: Thank you for this suggestion. This has been amended in the Discussion, line 368-371. XXX

12) L336-337: please clarify. The MAI is a valid tool to evaluate appropriateness, so why would it not be appropriate to evaluation appropriateness for a specific class of medications?

XXX Response to Reviewers/Editor: Thank you for this indication; we fully agree. We deleted this sentence and amended the respective paragraph (line 341-342). XXX

13) L349: 'onsite training had positive effects on…': no results data have been presented to support this. Please clarify.

XXX Response to Reviewers/Editor: Indeed, this was pointed out by the participants during the focus group interviews which represented the qualitative part of the study. Findings will be published separately (see line 123-124). We corrected this statement in the Discussion section (current line 385-387). XXX
14) L366: I would specify that this is a 'major' limitation (or at minimum, the 'main' limitation)

XXX Response to Reviewers/Editor: Thank you for this indication. We added “main” in the respective section (line 399). XXX

15) Another limitation is that - even though the number and types of outcomes evaluated was relatively important - that some other relevant outcomes were not measured. You could refer to the recently validated core outcome sets.

XXX Response to Reviewers/Editor: Thank you for this helpful suggestion. We added a statement referring to the core outcome sets (line 412-415). XXX