Author's response to reviews

Title: Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis

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Author’s response to reviews:

Response to reviewers Determinants of the range of drugs

We thank the reviewers for their detailed and constructive comments. We think we could improve the manuscript a lot in the revised version.

Response to major compulsory revisions suggested by Petra Denig

1. The definition of variation is cleared. We indeed focus on the variation within therapeutic drug groups (drugs consisting of various chemical substances, but used for the same condition). This is what Bjerrum and Bergman as the most important indicator. The text is adapted.

2. The reviewer asks why the number of prescriptions per patient is included at practice level and not at GP level. Indeed, we also would prefer to analyze this on GP level. Practically this is difficult to do because patients could not always be individually ascribed to a gp. Repeat prescriptions are often not to ascribe to a specific GP. Further patients in group practices do not always visit the same GP. Therefore we included this independent variable at practice level. For the dependent variable concerning the range of drugs, however, it was possible to analyze at GP-level because we only based it on the prescriptions that could be ascribed to a specific GP. We clarified this in the method section.

3. The reviewer writes that we state to easily that the correlations between the independent variables are moderate. The correlation with elderly (.29) and dispensing practice (.43) might point in the direction that the number of prescriptions per patient is in fact a proxy for having patients with more morbidity and more specialist prescriptions. The correlations are, however, below the threshold of .60, what is generally considered the threshold for risk of multicollinearity. The correlations with elderly and other indicators for the morbidity of the practice population remain far from this threshold. For dispensing practice the reviewer might have a point especially because the correlation with non-urban practice (all dispensing practices are in non-urban areas) is .55 and we know that in dispensing practices is more specialist prescription. Removing the dispensing practices from the analysis did not change the overall picture, however. We devoted attention to this in the discussion.

4. The reviewer criticizes some of our interpretations and conclusions:
   - The conclusion that the range is a useful addition to existing cannot be drawn from the mere fact that there is variation. We agree with the reviewer that this does not tell anything on quality. We therefore recommended further research into the relationship between the range and quality. In the discussion we changed 'useful' into the more careful 'promising', as we already did in the abstract and the overall conclusion.
   - The explanation 'That a broader drug repertory could increase the inclination to prescribe' is not based on literature, but refers to the theoretical notion that if a doctor has more therapeutic possibilities he will be more inclined to apply one. We clarified the sentence in the discussion.
   - 'When information from industry comes in a practice through one gp in a group practice, why would this be quicker in comparison to information that comes directly to a GP working single handed?' This is a misunderstanding due to unclear formulating from our side. We do not mean quicker compared to single handed practice, but quicker compared to his colleagues in the practice. We improved the phrasing.
   - There is literature to support the statement that working in group practices is often associated with a stronger esteem to colleagues. We took up two references here.

Response to minor essential revisions:

5. The introduction is revised. Repeating information is removed. The sequence of the references is
checked. The discussion is completed with references.
6. Bjerrum, Bergman, 2000 is referenced. Also other recent references are mentioned.
7. More systematic is reported which literature forms the basis of the different hypotheses. The hypotheses section is restructured.
8. 'GPs' pharmaceutical knowledge and information sources' is corrected in 'GPs' information sources'.
9. In the method section the factor analysis is clarified: the scales used were independent factors in the factor analysis.
10. The reviewer asks to explain that there was no significant variation at practice level in the empty model, but a strong clustering within practices in the full model. In general this is possible as a result of a reversed compositional effect.

Discretionary revisions:
11. We agree with the reviewer that it would be interesting to link the ranges of drugs prescribed to the range of drugs recommended in formularies. In fact we are doing this in a follow-up-project in which we link the formulary of the Dutch College of General Practitioners to our LINH database. In this article it is a step too far, however.
12. The selection of some ATC3 and some ATC4 groups is a bit arbitrary and leads to possible artifacts in subgroups with few drugs. We agree with the arbitrariness. Doing all analysis on ATC4 groups (with which we originally started) would have aggravated the problem of few drugs per group considerably. Aggregating everything to ATC3 would have created very heterogeneous groups. We have chosen for a trade-off. The sentence 'the percentage of available drugs was low in both antibacterials and antipsychotics shows that a low percentage of available drugs does not imply little variation ...' needs clarification because the reviewer says that two examples do not 'show' much. We added therefore the word 'automatically' after imply (which we meant in fact).
13. We did two-tailed testing when there was no directional hypothesis (see the footnote under table 2). We added a note to the analysis-section and controlled the manuscript to check whether we did this systematically. We clarified this in the method-section.

Response to reviewer 2 Muijrers

Major compulsory revisions

Background
The reviewer asks for a more comprehensive literature search, especially with respect to recent literature. Reference to the DU90% is missing.
We updated our literature search. Several references concerning the DU90% are included. Also, more recent literature concerning prescribing patterns is referenced.

The reviewer suggests to group the prescribing determining factors into five groups: general person-specific, pharmaceutical aspects, the effect of guidelines, the effect of information and education and the influence of the patient. We restructured the hypotheses-section partly following this suggestion. We had no information on pharmaceutical aspects and the effect of guidelines, however. Further we added the practice setting as a separate group.

Hypotheses
References have been updated as reviewer suggested.

The reviewer claims that the sentence 'Data for dispensing practices might also contain drugs that were prescribed by hospital consultants, which would result in a broader range' is not relevant because data of non-dispensing practices might also contain drugs initiated by hospital consultants.
We agree that with the reviewer. Data of non-dispensing practices contain also drugs initiated by hospital consultants that are continued by GPs as repeat prescriptions. But dispensing practice data also contain drugs of prescribed by hospital consultants in the outpatient clinic. Generally these data are not included in the electronic medical records of the GP. So (to our regret by the way) the sentence is relevant. We can clarify this further in the text, if the editor wishes but it would become very complicated for those not familiar with the Dutch situation.

Discussion:
As the reviewer suggested more attention has been paid in the discussion to the concept of the rage compared to other measures like the DU90% and the total number of prescriptions.
Minor essential revisions:

Hypotheses:
'Pharmaco-therapeutic consultations (FTO) is replaced with Pharmaco Therapeutic Audit Meetings (PTAM).

Results:
The reviewer suggests that table 3 may be redundant because of the moderate correlations. We did not follow this suggestion considering the remarks of reviewer 1 about the correlations and the adaptations following these remarks.

Response to reviewer 3 Verstappen

General
The reviewer is not impressed by the results of the paper although well defined. He does not see what the paper adds to the existing knowledge. The hypotheses do not underpin the hypotheses that a restricted range results in more quality and less societal costs.

Our answer to this is that testing the hypotheses that a lower range was not our research objective. Our research goal is to analyze variation at practice and GP-level and to look for factors explaining these variations. New compared to earlier research is that we looked at GP-level where earlier research only looked at practice level and that we took in consideration more explaining factors for example on the information sources of the GP and the composition of the practice. We tried to clarify what is new in our research better in the abstract and at the end of the introduction and in the discussion.

Further the reviewer claims that no attention has been paid to the role of the patient in the GPs' prescribing behaviour. We controlled, however, for characteristics of the patients like percentage elderly, percentage higher educated, percentage publicly insured (which is in the Netherlands a proxy for income) and percentage of non-western origin. So we took into account more patient factors than in any other research referenced in this article.

Background
The reviewer asks for more explanation regarding the fact in the Netherlands that many prescriptions are initially prescribed by hospital consultants but after that continued by GPs. This remark connects to the remark of reviewer Muijrers concerning dispensing practices. More attention has been paid to this problem in the discussion.

The reviewer is surprised that female GPs have a significantly lower range than male GPs. This must be a misunderstanding. There is no significant relationship between the GPs gender and the range as table 2 shows. We took gender in the analysis as a control variable because we did not suppose a direct relationship between gender and the range.

The reviewer thinks that data from dispensing practices show more variation in prescription ranges than non-dispensing practices. To our knowledge our research project is the first that related range to the variable dispensing/non-dispensing.

The reviewer does not agree with our hypotheses concerning group practices. He claims that there is much evidence that working in group practices means better adherence to guidelines and better cooperation. Research done so far into the range shows that group practices have a larger range than solo-practices. Our research shows, however, that if you look at the level of the GP, GPs in a group practice do not have a broader range than other GPs. The fact that GPs in group practice adhere better to guidelines could be an explanation for this. A remark and two references are added to the discussion.

The reviewer is not sure that more prescriptions always result in a broader range. We stated, however, that more prescriptions increase the chance of a wider range of diagnoses and therefore a wider range.

Methods
The reviewer regrets like reviewer Denig that the analyses only has been done for the overall-range. For a follow-up of this article it would be interesting to look at the subgroups.

The reviewer makes also a comment on the fact that we tested onetailed because the directions of the hypotheses was not clear. As said earlier we clarified the text on this point and we checked all hypotheses.
This resulted in two more hypotheses where we tested two-tailed (age and gender), because the direction of the hypotheses is unclear. This is corrected in table 2. Further, we maintained one-tailed testing because this is common when a direction is supposed.

The reviewer asks whether 'to be unidimensional in HOMALS-analysis and factor analysis' means that onetailed testing is allowed. Our answer is no; two- or onetailed testing is purely determined by the direction of the hypotheses.

Results
Reviewer states that the sentence 'the fact that the percentage of available drugs ... not imply little variation between GPs’is not a result but a statement. This statement is meant to be an observation of what can be seen in the table, but may be confusing. We rephrased the paragraph to avoid any misunderstanding.

The reviewer says as reviewer Muijers that table 3 can be skipped. Considering reviewer Denig’s remarks and the following adaptations we made we did not follow this suggestion.

The reviewer does not agree with the authors remark that the relationship between range and prescriptions per patient could be explained by the fact that a broader drug repertoire could increase the inclination to prescribe. We clarified therefore in the discussion why we see this as an explanation: a broader repertoire means more therapeutic possibilities. Further we added an additional explanation offered by the reviewer, namely the influence of specialist initiated repeat prescriptions.

The author criticizes our paragraph on group practices, which according to the author better adhere to guidelines. We agree with him, adapted the text and added references.

Conclusion
The reviewer argues that the range is not a promising concept because when prescribing volume is used, the range is already used. This is a matter of opinion. Although range and prescribing volume are clearly related we think it is a possible addition. It varies clearly between GPs and is related to known prescribing influencing factors like visits of the pharmaceutical industry. Further the measure can be used at group/subgroup-level, thus providing starting points for interventions.