Dear Mrs. Dumbreck

Manuscript ID BMJ.2014.022733 entitled "Systematic examination of drug-disease and drug-drug interactions from following recommendations in 12 UK national clinical guidelines"

Thank you for sending us this paper and giving us the chance to consider your work. We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest below. We are provisionally offering acceptance but will make the final decision when we see the revised version. The report from the manuscript meeting, the comments from the reviewers and general requirements for submission are available at the end of this letter.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from today's date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Yours sincerely

Dr. Jose Merino
Editor

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Rafael Perera (statistical consultant), Emma Parish, Tiago Villanueva, Rebecca Burch, Georg Roeggla, Alison Tonks, Wim Weber, José Merino

Decision: provisional acceptance

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

• We found the research question interesting. The paper identifies some important limitations of clinical guidelines. The findings also highlight potential pitfalls of using guidelines to develop quality indicators, as some patients will not be eligible for treatments recommended in the guidelines because of their comorbidities. In addition, many conditions tend to cluster in the same individual. We encourage the authors to expand on these ideas as appropriate.
• We ask the authors to add some clinical examples to illustrate their main conclusions. We suggest including several patient vignettes, one or two for each index condition, perhaps in a separate box that appears along the text. Each vignette can describe a real patient, identifying relevant comorbidities, and describe how competing guidelines lead to drug-drug and drug-condition interactions in that particular patient. These examples will make the paper more relevant for clinicians.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Referee comments**

Reviewer(s)' Comments to Authors:
Reviewer: 1

Recommendation:

Comments:
Dear Editor

thank you for making me review this manuscript. the topic addressed by the authors is relevant, current and of interest for the Readers. It is a common opinion amongst GPS, geriatricians and also other specialists that applying guidelines to people affected by multimorbidity can be harmful.
Drug-drug interactions are especially Dangerous as they are not Always taken into consideration and they increase both with the number of prescribed drugs and the age of the patients. Gathering the attention of the medical establishment on this problem could improve prescription in people with multimorbidity

The paper is well-written and clear and i do not have any major issue to rise.
I have some suggestions:
1. the authors mention several times that DDIs may be Dangerous as they can cause adverse drug reactions. They may add in the discussion some papers that showed the effect of DDIs on ADRs. Recently, we got a paper accepted and in press in a few days on EJIM evalauting all ADR reporting forms affected persons aged 65+ years collected by the pharmacovigilance of one of the main hospitals in Italy during 2013. Amongst all the ADR reporting forms (n=1014) , 343 affected older adults. The most frequent ADRs were: haemorrhages (n=122, 35.5%), allergic reactions (n=56, 16.3%) and elevated International Normalized Ratio (INR>6, n=54, 15.7%). A total of 912 DDIs were found; one third of them were contraindicated or major and 31.5% of them potentially contributed to ADRs; of these, the most frequent were: warfarin and heparin (contraindicated, n=5); warfarin and a statin (major, n=38); warfarin and a proton pump inhibitor (moderate, n=40). At least one DDI contributed to 66 haemorrhages out of 122 (54%) and to 41 elevated INR out of 54 (76%). i think that it is important to show the Readers how harmful DDIs could be.

2. The use of a computerized prescription support system that evaluates prescriptions from the appropriateness to the risk of DDIs and ADRs should be mentioned as a good help for clinicians when dealing with patients affected by multiple chronic diseases. the authors can mention different references such as the following one (Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck(®)).
Ghibelli S, Marengoni A, Djade CD, Nobili A, Tettamanti M, Franchi C, Caccia S, Giovarruscio F, Remuzzi A, Pasina L. Drugs Aging. 2013 Oct;30(10):821-8)

Finally, I think that this research topic should have the highlight that it deserves in the medical literature.

Additional Questions:
Please enter your name: Alessandra Marengoni

Job Title: Medical doctor, assistant professor

Institution: University of Brescia, Italy

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
Dear editor and authors.
I enjoyed reading this manuscript aiming to identify the number of drug-disease and drug-drug interactions for medical conditions with (NICE) clinical guidelines. I would like to congratulate the authors in their efforts as I find the study well designed and performed, the manuscript generally well written and results valid. In terms of readability I struggled a while to get my head around the methods and results several places concerning the different guidelines and conditions (e.g. page 3 line 19-21, abstract). I am not sure how this could be improved but perhaps editorial staff could help if others also find this difficult to understand. Another general issue is the authors choice of focussing on number of times a drug was recommended for the index conditions which I found a bit confusing. An alternative -or complementary- approach, would be to relate the findings to the number of recommendations in the guidelines. To me this would be valuable information (e.g. for how many/ what proportion of the recommendations in the diabetes type 2 guideline was there a problem with interactions). Again, if more people than myself struggle with understanding the results this would be something to consider.

I would I think the major issue is the newsworthiness and clinical relevance for the target audience in terms of publishing in the BMJ as problems with guidelines related to multimorbidity and polypharmacy are well recognised in the medical community and what we need most of all are solutions. The added value of this paper would be to either provide new and trustworthy evidence concerning problems with current ways of covering multimorbidity in guidelines or alternatively to provide new evidence guiding next steps for guideline developers. In my opinion these findings are trustworthy, interesting, newsworthy and informative for such next steps. Indeed they do provide interesting guidance for those of us involved in trying to improve management of comorbidity in guidelines authoring and dissemination (e.g. GIN multimorbidity group).

I have the following minor comments for the authors to consider:
1. I am confused about what the authors label as first and second line treatment in NICE guidelines. From the discussion these seem to reflect strong and weak recommendations. I would suggest authors initially refer to new standards and systems for trustworthy guidelines which require among other virtues that strength of recommendations are provided. Indeed, NICE applies the GRADE system and should separate between strong and weak recommendations. The implications for comorbidity are in my view important as weak recommendations reflect a fine balance between benefits and harms (and/ or uncertainty) and represent suggestions which warrant balanced considerations not only of values and preferences but also issues like comorbidity when applying the recommendations. Strong recommendations without mentioning of interactions would to me be a greater danger as these are "just do it" recommendations, applying to all or nearly all patients. The authors could consider discussing these implications to a somewhat larger extent than in the present discussion page 10.
2. Page 7, line 16 (results): In general I was a bit confused and put off by these results in such a prominent place in the results section. I would suggest authors reconsider the sequence of results a la the abstract. I was particularly confused by "....in the three exemplar clinical guidelines for type 2 diabetes". Did this study include more than one study on diabetes?
3. Page 10, line 42 (discussion): I find the authors overly optimistic in terms of guideline panels accessing primary care databases to determine prevalence of comorbidities etc. I would suggest they temper their enthusiasm a bit.

4. Page 11, line 30: Here it would be good to refer to trustworthy guidelines and GRADE system to strengthen the rationale.

Additional Questions:
Please enter your name: Per Olav Vandvik

Job Title: Associate professor

Institution: Institute of Health and Society, Faculty of Medicine, University of Oslo

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I am executive director of Making GRADE the Irresistible Choice (MAGIC) research and innovation program and non-profit organization (www.magicproject.org). We have developed a guideline authoring and publication platform (MAGICapp) to facilitate the authoring, dissemination and updating of evidence summaries, decision aids and trustworthy guidelines in web-based interactive and user-friendly formats. I am also a membe of the Guideline International Network working group om multimorbidity. I do not consider any of these engagements to represent an intellectual or financial conflict of interest with implications for this peer-review.

Information on revision the format and content of the article and submitting the revision

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model). The print and iPad BMJ will carry an abridged version of your article. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using the template downloadable at http://resources.bmj.com/bmj/authors/bmj-pico. Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licenses and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000

on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee. We have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this). You need do nothing now.

4. How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

3. A statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form for publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

4. Signed patient consent form(s), if the article gives enough personal information about any patient(s). This sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

5. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

6. Contributorship statement+ guarantor (see http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship)

7. Transparency statement: a statement that the lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies are disclosed.

8. Copyright statement/ license for publication (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)

9. A data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors. The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option

10. Funding statement (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

11. Statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements). For studies funded or sponsored by industry, a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. Also include, in the cover letter, assurance that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice and, in the list of contributors, the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

12. Patient-centered research statement. For studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centeredness. In the Methods section, please state whether patients, service users, careers, or lay people were involved in the design of this study, development and selection of outcome measures, and participant recruitment and study conduct. In addition, describe any plans to disseminate the results to study participants. For clinical trials, describe whether you assessed the burden of the intervention on patients' quality of life and health and what evaluation method was used; in the results section please describe what you found.

13. Please ensure the paper complies with The BMJ's style., as detailed below:

a. Title: this should include the study design e.g. "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials

can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (e.g. 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study: OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, e.g. RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers e.g. STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

AUTHOR RESPONSE

Thank you for asking us to resubmit this paper, and for the helpful comments from the reviewers and the manuscript committee meeting. Our responses and revisions are detailed below.

Please note that our NIHR HS&DR programme manager has raised a query about the licence:

"Your publication submitted to BMJ has been reviewed and it would appear that within this document you have granted an exclusive licence on a worldwide basis to the BMJ Publishing Group. Unfortunately this contravenes the contract in place with the DH for this work as this material is subject to 'Crown Copyright'. If the BMJ does not offer an option to have this work acknowledged as 'Crown copyright' only a non-exclusive licence may be granted as the Authority need to ensure that the work is copyright of Queen's Printer and Controller of HMSO."

I would be grateful for advice from the BMJ regarding license and NIHR funding, to advise on the best form of words to acknowledge as 'Crown copyright' to ensure that the work is copyright of Queen's Printer and Controller of HMSO. Meantime we have removed the licence statement from the manuscript and would be grateful for your advice about how to indicate publishing under a CC BY license.

Yours sincerely,

Siobhan Dumbreck on behalf of all authors

Reviewer 1
1. Suggestion to add some papers that show the effect of drug –drug interactions on adverse drug events to show the readers how harmful these interactions could be.
Done – included a statement in the second paragraph of introduction "A significant proportion of ADEs causing harm are drug-drug interactions." Referencing:
Marengoni A, Pasina L, Concoreggi C, et al. Understanding adverse drug reactions in older adults through drug–drug interactions. European Journal of Internal Medicine 2014;25:843-846
Schedlbauer A, Prasad V, Mulvaney C, et al. What evidence supports the use of computerized alerts and prompts to improve clinicians' prescribing behavior? Journal of the American Medical Informatics Association : JAMIA 2009;16(4):531-8

2. Computerized decision support for prescribing should be mentioned.
Done - included in the second paragraph of introduction "Systematic reviews have shown that electronic alerts and prompts demonstrate benefit in improving prescribing behaviour or reducing error rates [10]. But despite the availability of computerised decision support, ADEs as a cause for seeking ambulatory care have increased…

Reviewer 2
1. Regarding readability page 3 line 19-21,abstract
Done – added sentence to the third paragraph of the abstract "Following recommendations to prescribe in 12 national clinical guidelines would result in a number of potentially serious drug interactions".
2. Confusion about labelling of first and second line treatment in NICE guidelines.
Rewording of this in second paragraph of Methods.
3. Page 7 line 16 results
Reduced prominence of these results by changing sequence as per reviewer's suggestion
Done – rewording of paragraph 2 of Results, and inserted table 2.
4. Page 10, Line 42 (discussion)
Temper enthusiasm regarding optimistic in terms of guideline panels accessing primary care databases to determine prevalence of comorbidities etc
Done – rewording of 7th paragraph of Discussion, from "it is now reasonably straightforward" has been changed to "there is the option"
5. Page 11, line 30: refer to trustworthy guidelines and GRADE system to strengthen the rationale.
paragraph 8 of discussion now clearly states…… "and better understandings of harm and the implications for the extrapolation of trial findings to real-world populations will need to be systematically incorporated into existing guideline development frameworks like GRADE [41]"

Editorial committee
To make the paper more relevant for clinicians two patient vignettes have now been included, referred to from the discussion with an indication of how commonly the conditions involved are comorbid, which describe a relatively simple and a more complicated set of drug-drug and drug-condition interactions. This also shows that some patients will not be eligible for treatments recommended in guidelines because of their comorbidities, to highlight the limitations of clinical guidelines for single conditions.