Author’s response to reviews

Title: Strategies for Eliciting and Synthesizing Evidence for Guidelines in Rare Diseases

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Re: BMRM-D-18-00004

Strategies for Eliciting and Synthesizing Evidence for Guidelines in Rare Diseases

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Dear Dr. Puljak,
We thank the reviewers for their thoughtful comments and the time put into this review. We also appreciate the opportunity to resubmit our manuscript. Please find our detailed responses below.

Technical Comments

No co-authors email address

Email addresses were provided for all authors – these have now been removed

Reviewer 1

BACKGROUND

1. In the background the authors defined the rare disease citing NIH and EU reference. However, the introduction of the term 'rare' could have been clearer and decisive. A disease, which is rare to one population may be endemic to another population, should those diseases be considered as rare or non-rare disease? A bit of explanation would help readership of the journal grabbing the construct.

We have more clearly laid out that the quoted numbers are official definitions, used to guide policy and funding decisions. We have added the reviewer’s excellent point about the “uneven” nature of rare diseases, with this statement: “Moreover, a disease defined as rare in the general population may be endemic to specific smaller populations, conferring disproportionate impact on these communities.”

2. "There are thought to be over 7,000 rare diseases." This kind of blunt statement requires referencing; the authors should take care of this issue in the rest of the manuscript. Wherever a statistics is provided or an information used that is generated from other's research, or taken from credible source.

This statement was taken from an NIH document, however we have opted to remove it. It does not add to the manuscript, and as stated by the reviewer, is fairly blunt!

3. page 3, Line 27 " Well powered studies are rarely done because of difficulties in …….." It should be rather 'adequately' powered. …

Corrected – thank you.

4. Barriers to Evidence Generation in Rare Diseases may also be contributed by lack of funding due to inadequate political will, because of the rarity of the condition. Author may consider discussing this as well.
We previously avoided discussing the policy and political barriers to this research, however have inserted a brief paragraph alluding to these as the reviewer feels they would add to the background.

“Most rare diseases are not a focus for policymakers, funders, and researchers in many countries. Pharmaceutical companies may invest significant financial resources in bringing orphan drugs to the market, but often struggle to recover costs through sales.[7] Without Orphan Drug Regulations and cross-sector sponsorship initiatives, there are few economic incentives to develop treatments for rare diseases.[8, 9] And as the number of individuals affected by a rare disease is, by definition, small, a critical mass of people who can advocate for research and development may not exist.”

5. I did not quite understand the aim of the study presented in the page 4 line 17-21. "Our aim is to "explore" and "overcome" the barriers identified above using a dedicated framework for guideline development in the field of rare diseases, as proposed by the RARE-Bestpractices Working Group. In method section clear description is needed how the exploration is taken place and the overcome owas achieved

Agree that this was unnecessarily confusing. Our aim was to take strategies proposed by the Working Group, and pilot them in three guidelines that members of our group developed. We have stated this far more simply.

“Our goal was to determine if: a) the novel strategies for eliciting and synthesizing evidence can be feasibly implemented in guideline development for rare diseases; and b) if the framework helps overcoming all or some of the barriers to guideline development described above.”

6. The authors must introduce the "RARE-Bestpractices Working Group" in the background before incorporating it in the study aim.

Thank you – this has been done.

7. While mentioning the aim, authors would say what they have aimed at not what they have done. Methods section is the place where the author should say what and how they have done it. "We have piloted the suggested framework in three specific guideline development processes undertaken in three different rare conditions."

Thank you – this has been done.

METHODS
8. Methods section should be re-written entirely. In this section the authors should clearly describe what they have done and how, in such a manner that, a reader can replicate the result following the methods as instruction. I am a bit confused what the authors have done.

Did the authors develop the guidelines or they have appraised the guidelines developed by others, I so, what are the steps and process they have followed? If as a reviewer I fail to comprehend, so will do the readership of the journal.

We have revised the methods section and made it clear that all three guidelines were developed by coauthors of our paper. This was not an appraisal of others’ work, but a road test of a proposed framework. We have made it clear which strategies were piloted in which guidelines at the end of the Methods section.

9. In method section clear description is needed how the 'exploration' is done and the 'overcome' was achieved. Description of those guideline is not enough and that is not the work of this study, those are some else's. The authors should describe their work's method more.

The work we are describing is the methodologic work done by members of our group in service of developing these three guidelines. We have attempted to make this clearer in the revised manuscript, and we thank the reviewer for helping us troubleshoot this.

8. 'Three guidelines are considered for the study' is a poor starting sentence of the method section. "Considered for doing what and how?" Is more important for the readers to know.

This sentence has been removed – agree it is unhelpful. Now the section methods starts as follows:

We piloted the suggested framework in three specific guideline development processes undertaken in three different rare conditions. All three guidelines were coauthored and developed by authors of this report. Essentially, all three projects were at the same time and explicitly aiming to achieve a double goal: produce a true guideline to be used in clinical practice and implement our framework to overcome expected barriers in guideline issuing in rare diseases. The most involved guideline members focusing on the latter goal where the methodologists, whilst the clinical panel members acted more as user trying out and experiencing the impact of our framework.

9. Page 5 lines 26 onwards, the authors described principles of GRADE, These sort of generic information and example could be brief or can go to appendix if needs to stay. Most Importantly, I now am in the end of the methods, I could not yet figure out what the authors have done and how? Same puzzling situation may happen to the journal readership.

Thank you – understood! We have reworded this to make it more clear that GRADE is a strategy developed originally for common diseases. What we are testing – the working group
framework – is a collection of strategies that is complementary to, but not part of, GRADE, and is intended to become a GRADE extension in the future. The paragraph has been reworded as follows.

Most of the applications of GRADE to date have been outside the field of rare diseases, and it is unproven if GRADE can be efficiently applied to rare diseases. For this study, we utilized the RARE-Bestpractice Working Group’s pilot framework for applying GRADE to rare disease guidelines, applying elements of it to all three guidelines and assessing its feasibility and practicability.[18] These rare-disease specific elements were as follows:

RESULT AND DISCUSSION

10. Result should say what authors have found based on the work have done as described in the methods section, in discussion section they can elaborate those. I would tabulate the finding for convenience of the readership.

We have now highlighted right from the start of this section that we were able to meet our aim and fulfill what we laid out in the methods section. We have also more clearly highlighted which elements of the framework were used in which guideline, though have opted not to tabulate our findings.

11. In page 10, line 18 onward "Another strength of our study is its confirmation that non-experimental data (including observational data and qualitative evidence) ..........." Not sure, what is the previous strength … previous paragraph was on different topic….

We thank the referee for pointing out the unclear separation of the two points. We are confident we have now made clear that the first is using observational evidence of various quality and qualitative evidence FROM THE LITERATURE, while the second is GENERATING NEW EVIDENCE through standardized expert reporting forms.

12. In the last paragraph of discussion page 11, line 7, please remove the link and cite the reference.

The links have been removed. As these are international research groups and not manuscripts, we have chosen not to use formal referencing.

13. There should be section for limitation of the study.

We attempted to outline limitations in the final paragraphs of the discussion. We have highlighted this more clearly.
“There were clear limitations to our work, and to the RARE-Bestpractice Working Group’s framework. Qualitative research did provide ….”

“Finally, our study identified limitations to the use of expert-based evidence. Guideline developers….”

CONCLUSION

1. "After theoretically exploring the barriers to issuing guidelines on rare diseases, we proposed an operational approach consistent with GRADE.[15] We have now applied this approach in three specific rare conditions.[19] We have confirmed that priority setting, question generation and prioritization, and outcome identification and ranking, all pursued with extensive involvement of patients and experts are key steps.” …… I would not consider it as a conclusion. In the conclusion, the authors briefly describe the punch message they have discovered/invented/generated in their study, not others'. Please consider rewriting.

Have rewritten this – thank you!

2. Last paragraph of the conclusion page 11, line 31 onwards … looks like recommendation!!.

This was intentional, as we feel our work suggests avenues for further research. We have reworded the paragraph to make it clear that we are recommending something that has grown out of our conclusion.

Thank you for considering this manuscript for publication. Please contact me if you have any further suggestions or concerns.

Sincerely,

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