Reviewer’s report

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

Version: 0 Date: 01 Sep 2018

Reviewer: Md Karim

Reviewer’s report:

The manuscript titles "Strategies for Eliciting and Synthesizing Evidence for Guidelines in Rare Diseases" is an effort to address a very pertinent issue and is likely to contribute the Mitigating the challenges, in creating guidelines for rare diseases. I congratulate the authors for taking the daunting task. The topic has its gems, however the manuscripts requires to be written in a scientific manure. Below are some comments to the authors.

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.

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.

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

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.

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

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

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.

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.

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.

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.

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.

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….

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

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

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.

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

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal