Author’s response to reviews

Title: Opportunities and Challenges for the Inclusion of Patient Preferences in the Medical Product Life Cycle: A Systematic Review

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Author’s response to reviews:

Leuven, March 1st, 2019

To the Editor and Reviewers,
Dear Dr. Shaban-Nejad,

Dear Dr. Christopher (reviewer 1),

Dear Dr. Pizzi (reviewer 2),

Dear Dr. Li (reviewer 3),

Hereby we would like to submit a revised version of our paper, entitled 'Opportunities and Challenges for the Inclusion of Patient Preferences in the Medical Product Life Cycle: A Systematic Review', by Janssens et al. for publication in BMC Medical Informatics and Decision Making.

We would like to sincerely thank the reviewers for their time and valuable suggestions, which we believe helped us improving the readability and quality of our paper. We implemented the following main changes, by which we addressed comments raised by the three reviewers: i) we restructured the results according to the review questions, ii) we included specific examples in the results and discussion section and iii) we revised the format of the tables, which we believe increased their readability.

Responses to the reviewers' comments are detailed below per reviewer in bold.

Yours sincerely,

On behalf of the co-authors,

Rosanne Janssens

Reviewer 1: accept after discretionary revisions

The review aimed to understand the potential roles, expectations, concerns and requirements associated with the use of patient preferences in industry, benefit-risk assessment, and reimbursement decision-making. This is an important area of research as FDA and other regulators seek to understand the potential use and value of patient preference information, but also need to be assured of the quality and validity of the patient preference data.
The description of the selection criteria and data analysis was appropriate and well-suited for the type of study described.

The authors stated that they want to understand the desires, expectations, concerns and requirements regarding the use of patient preference information across the medical product development life cycle. However, it seems the majority of text on the results focuses on concerns regarding the use of patient preference information in industry, BRA/MA decision-making, and HTA/reimbursement. This is valuable content, but additional context as to the expectations of this information would be helpful. Why are these groups seeking patient preference information? What do they hope to get out of it? That context will help the reader understand the concerns and recommendations as presented.

Thank you for these suggestions. We agree it is important to not only highlight current concerns and requirements but also the added value, reasons and positive expectations related to patient preferences in decision-making. We restructured the results as proposed by reviewer 2. The new structure integrates the results previously reported per decision-making context, now per review question: i) what potential roles do PP have in the MPLC and what are reasons to use them, ii) what is expected to happen when PP are used in the MPLC, iii) what concerns arise for the use of PP in the MPLC, and iv) what is needed in order to use PP in the MPLC. We believe that this new structure highlights more clearly the added value of using PP, reasons to use preferences and expectations regarding preferences, as it has separate sections on these topics (i and ii). We furthermore adapted the format of the tables following the suggestion from reviewer 2, which we believe also addresses this comment; we believe the revised table 2 and especially table 3 now more clearly describe the rationale for using preference studies.

The authors may consider adding appropriate examples from the literature where each of these groups used patient preference information in a decision-making context. If such examples exist, they would help the reader understand the use of this information. I appreciate the discussion about requirements to move the field forward and hope that researchers take on the identified topics for future research.

Thank you for this valuable suggestion; we agree adding examples would help readers understand the context of the review and the results presented. Therefore, we added examples (Ho et al., Chow et al., IQWiG, Morel et al.) in the results section and highlight and discuss an example (Evers et al.) in the discussion section, by which we also address a comment raised by reviewer 2.
Reviewer 2: major revisions

Thank you for the opportunity to review this article "The Promise of Patient Preferences in the Medical Product Life Cycle: A Systematic Review." Overall, the issue of patient engagement and incorporation into the health technology assessment process is critical and timely. Thus, this article is likely to be of high interest to a subset of readers concerned with regulatory approval of new drugs but also other health-improving technologies. However, the context of the review is absent. There is no discussion of PREFER and how this project fits into the broader initiative. In addition, the author list for the paper is inordinately long and there is no clear rationale. Was this group a task force or advisory committee to Erasmus on the issue of patient preferences? Were all of these individuals involved in the conceptualization and development of the paper? What is the rationale for the diverse makeup of the author panel and how were these individuals identified for engagement in the review?

Thank you for your careful and critical review of our paper. Please find below our detailed response to the comment regarding discussion of the PREFER project. Regarding the authors of the paper, the amount and diversity of this author list originates from the collaborative nature and multi-stakeholder approach that we took for this research as part of the PREFER multi-stakeholder project. PREFER is a large public-private partnership consisting of academic partners, industry partners and public partners. These authors were selected based on the ICMJE criteria; they all substantially contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafted or critically revised it for important intellectual content; and gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition, though the questions to be addressed by the review are impactful and well stated, the Results section does not clearly link back to the questions. It would be best if the Results section had subsections which addressed how each of the review questions were answered. In addition, the Results content is quite high level/general. It would greatly benefit from specific examples woven in to emphasize key points. It seems that a number of the references relate to specific diseases (cancer, cardiovascular disease, diabetes, et al) and it would enhance the discussion to use these diseases as cases to illustrate key findings.

Please see our detailed response on how we restructured the results section below. Regarding the addition of examples: thank you for this valuable suggestion, we agree adding examples would help readers understand the context of the review and the results presented. Therefore, we added examples (Ho et al., Chow et al., IQWiG, Morel et al.) in the results section and discuss an example (Evers et al.) in the discussion section, as also suggested by reviewer 1.
The most useful parts of this paper are the Results tables however the emphasis of these tables is seemingly as weighted on the references as the text content. This presentation is a bit atypical and the content of the tables gets lost. It would be best if the tables were formatted to emphasize the content.

Thank you for this valuable comment; we agree the information in the tables could be better emphasized and therefore reformatted all tables so that the emphasis is placed on their content rather than the references.

Specific comments:

" Title:

o Suggest omitting "The Promise" from the title of the paper because this review focuses on currently available information and not the future promise of patient preferences. We agree with this suggestion and adapted the title to: "Opportunities and Challenges for the Inclusion of Patient Preferences in the Medical Product Life Cycle: A Systematic Review". We believe this title accommodates for all the described results, relating to both the potential roles and reasons to use PP (i.e. the opportunities) and the remaining concerns and general requirements (e.g. the lack of guidance, methodological hurdles: i.e. the barriers). This title also aligns with what is stated at the end of the introduction: "Insights of this review show opportunities and challenges for the use of PP in decision-making".

" Background:

o Define MPLC prior to using abbreviation (Page 6, Line 138) We agree with this comment and now provide an explanation for MPLC after first use on line 107.

o Define how review questions were derived. Why are these the focus? (Desires, expectations, concerns, requirements) Thank you for this suggestion; we agree it is useful to describe our rationale for these review questions and therefore added a separate section describing the context of the review in the method section on p.6, line 139.

o Describe a brief description of PREFER including objective and goals of the program. We agree it is useful to describe our rationale for these review questions and therefore describe PREFER and its objective in the abovementioned new separate section on p.6, line 139.

" Results:

o The tables provide value information which is easy to process, however the results section provides redundant information. Remove redundant information from the results sections
that is reported in the tables. Thank you for this comment, we agree and have carefully reviewed and restructured our results section (please find a description of this new structure below). Given the new structure of this section and our careful review, we are confident we have removed duplicating information.

- Results need to be reported as per the objectives of the study. Thank you for raising this critical but valuable point. We agree that presenting the results per review question, as opposed to the decision-making contexts of focus in this review, is a useful way of presenting our results. We revised the results and integrated them according to the review questions: i) what potential roles do PP have in the MPLC and what are reasons to use them, ii) what is expected to happen when PP are used in the MPLC, iii) what concerns arise for the use of PP in the MPLC, and iv) what is needed in order to use PP in the MPLC. We are convinced that this increased the readability of our paper while also allowing us to condense the results by removing duplicating results.

" Tables/Figures

- Some figures in appendix aren't numbered, titled or referenced

- Figures after figure 1 do not provide valuable information to the readers. They appear to be re-purposed from a slide presentation and are not clearly linked to the paper content. Suggest omitting them. We would like to thank the reviewer for indicating this instance of duplicating information. We agree that this information is presented in the tables and we therefore removed all figures after figure 1.

Reviewer 3: major revisions

Major comments:

" Brief introduction of 'medical product life cycle' should be given in the background section. Thank you for noticing this lack of explanation of this term; we agree with this comment and now provide an explanation for MPLC after first use on line 107.

" Have you followed any guideline of systematic review (e.g. PRISMA)? The PRISMA flowchart template was used (figure 1) and the PRISMA checklist was used for reporting the review. However, as the PRISMA checklist focusses on the reporting of systematic reviews evaluating clinical trials and evaluations of interventions, which was not the aim of the current review, we found that the following elements of the checklist were not suited for our review, and hence did not apply them for reporting the review: 12, 13, 15, 16, 18, 19, 20, 21, 22 and 23.

" Have you assessed the quality of included documents? Peer-reviewed literature should have higher quality than grey literature. Thank you for raising this point. We agree that if
relevant and appropriate quality criteria are available, quality assessment is an important step of a systematic review. However, we kindly disagree that peer-reviewed literature should receive more weight than grey literature for answering the review questions in the present review, i.e. we kindly disagree that peer-reviewed versus grey literature would be a good quality criterion for our review. In our case grey literature included regulatory documents (published by the European Medicines Agency or the US Food and Drug Administration), HTA reports and EU funded IMI deliverables (project reports), which contained extremely valuable information for answering our review questions. Following this comment of the reviewer, we found it important to clarify that the documents that were part of grey literature in our review were not found on blogs, newspaper articles etc. Therefore, we now clarify the term 'grey literature' in the methods section on line 165 and further on line 175 by stating what types of documents these were. This lack of relevant and meaningful quality criteria for our review is also the reason why we did not formally appraise the literature through the use of existing appraisal techniques. Further, although we did search for existing appraisal techniques, no technique was found that would be able to appraise the different types of literature included: original research, (systematic) reviews and grey literature.

" It is recommended to conduct a sensitivity analysis. For example, are the results robust if only including high quality literature? The lack of relevant quality criteria in our review, as explained above is also reason why we do not believe it is relevant to run sensitivity analysis based on such criteria.

" Writing. Some paragraphs are too long. Thank you for this comment. We agree that condensing the text would improve the readability of the paper. We condensed the results section by removing information already given in the tables. Additionally, as we agree with reviewer 2 that presenting the results per review question, as opposed to the decision-making contexts of focus in this review, is a useful way of presenting our results, we revised the results and integrated them according to the review questions: i) what potential roles do PP have in the MPLC and what are reasons to use them, ii) what is expected to happen when PP are used in the MPLC, iii) what concerns arise for the use of PP in the MPLC, and iv) what is needed in order to use PP in the MPLC. We are convinced that this increased the readability of our paper while also allowing us to condense the results by removing duplicating results. Finally, as we felt the results section describing the concerns related with using patient preferences would also be clearer if given in a table, we created an additional table 4 listing the concerns earlier given in text format. This helped reducing word count further. Reviewer 1 and 2 also suggested the addition of specific examples in the results. These actions altogether reduced the word count of the results section from 1836 to 859.
Minor comments:

"Why January 2011 is selected as the starting period? Thank you for raising this point. This date was chosen so that included documents reflect contemporary issues related to PP. This explanation was added in the methods section on line 160 and 184.

"There were 2 researchers while 3 names were given. Thank you for this comment, we agree that this phrasing was confusing. The selection was done by three researchers (RJ, EvO, CW), but each publication was screened by 2 reviewers. We therefore clarify this now in the methods section on line 168 by stating: 'First, title and abstract of peer-reviewed publications and the table of contents or headings of grey literature were screened for relevance to the review questions and exclusion criteria by three researchers (RJ, EvO, CW). Each document was independently screened by two researchers and disagreements were resolved by discussion.'