Author's response to reviews

Title: Setting an Agenda for Comparative Effectiveness Systematic Reviews in CKD Care

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Author's response to reviews: see over
Dear Editorial Committee,

We respectfully resubmit our Correspondence Article MS #5502236647093322 that is a 2nd resubmission to BMC Nephrology titled “Setting an Agenda for Comparative Effectiveness Systematic Reviews in CKD Care”. We greatly appreciate the comments of the three reviewers, and have made an effort to respond to each comment point-by-point.

We hope our response is acceptable to the editors and the reviewers and that our manuscript is now acceptable for publication. However, we are happy to make any additional changes you deem necessary.

**Point-by-Point Response to Concerns**

Referee 1/Comment 1:

*General Comments:* The manuscript reports on the process of determining priority topics in CKD care for future systematic reviews. Topic prioritization is of great importance to enhance efficiency and pertinence of the CER research enterprise. Recently, stakeholder involvement in the prioritization of research questions for systematic review and for new research endeavors has gained support as it is thought to contribute to the relevance and salience of the output. The authors embarked an independent, explicit process, assisted by a stakeholder panel. Authors and stakeholders have expertise in the domain of CKD. The paper is well written and the limitations section is transparent. Nevertheless, this type of a stakeholder driven approach may be considered a ‘social experiment’. Since still relatively new, experience with this process and its limitations is valuable to share and review. Therefore, I believe it is worthwhile to publish this paper, but also to highlight the challenges of this process. I hope the authors will consider my thoughts about the limitations of the process to facilitate quality improvement of such efforts going forward.

*Limitations:*

1) The development of the preliminary evidence map followed broad epidemiological concepts rather than an assessment of needs and knowledge gaps. For example, there is a Kidney Disease Improving Global Outcomes guideline on hypertension in process with extensive evidence review addressing topic 20 (hypertension, under progression). This topic was still ranked as the second highest priority topic, although de novo systematic reviews are not likely to provide major new insights at this point. Other topics on the list, such as acute kidney disease, anemia, dyslipidemia, bone/mineral disease and nutrition are also the subject of recent or ongoing evidence based clinical practice guidelines. Thus the rationale for including these topics in the topic list for consideration by stakeholders is not clear.

*Authors’ Response:* We agree with the reviewer that we employed broad epidemiologic concepts relevant to the natural trajectory of CKD as a heuristic for categorizing the topic areas. Further, we consider our stakeholder engagement process to have been ‘an assessment of needs and [perceived] knowledge gaps’ in the study of CKD. We are aware that a number of the topics our team preliminarily identified, and that stakeholders later selected as ‘high priority’ are the
subject of recent or ongoing evidence based practice guidelines. We identified topics \textit{a priori} without regard to whether they were the subject of ongoing reviews. We reviewed existing practice guidelines in our topic identification process, but did not limit our topics to those not already included in these guidelines, primarily because knowledge gaps often remain after guidelines are published (i.e. concerning specific therapies for specific patient populations). Because of this approach, we may have identified topics that were already undergoing systematic review. We have revised the methods section in an attempt to clarify our approach, by now stating on page 6, paragraph 3: \textit{“We identified topics without regard to whether they were the subject of ongoing reviews.”} We have also revised the discussion of the potential limitations of our project to include, on page 13, paragraph 2: \textit{“For instance, we developed the map and topic lists via iterative discussions prior to obtaining stakeholders’ input, and without regard to ongoing systematic reviews, which may have influenced the range of the final list of topics that the stakeholders ranked.”}

\textbf{Referee 1/Comment 2:}

2) The example questions predominantly consider kidney outcomes rather than all relevant outcomes in individuals with or at risk for CKD. For example, a question related to topic 3 (diabetes control and prevention) asked: What is the comparative effectiveness of diabetes management on CKD incidence? Kidney disease incidence is important but has to be reviewed in the context of many other outcomes of importance to individuals with DM, like CVD, neuropathy, infections. Similarly, most topics for ‘progression’ (Topics 13-32) specify the outcome of ‘slowing CKD progression’. Given the high burden of comorbidity, especially CVD, and frailty of the large number of elderly CKD patients, this is a narrow focus.

\textbf{Authors’ Response:} We agree that the example questions we have listed are primarily kidney outcomes, while numerous other important outcomes exist and are understudied in CKD patients. Similarly, these other topics may warrant CER systematic reviews. To clarify our approach, we have added the following footnote to Table 2, regarding our example questions, \textit{“Example questions are intended to illustrate ways in which CER topics can be framed, but are not intended to reflect questions themselves.”}, and have added the same statement to the first mention of Table 2 on page 9, where we state, \textit{“Table 2 lists the 46 topics (grouped by domain, in no particular order) and example CER questions. The example questions are intended to illustrate ways in which CER topics could be framed, but they are not intended to limit the range of CER questions which could be asked regarding CER topic areas.”}

\textbf{Referee 1/Comment 3:}

3) The stakeholders have important qualifications and representation, but the process of selecting them towards balancing the panel across relevant stakeholder categories or perspectives is not described. The rationale for the number of stakeholders is not provided.

\textbf{Authors’ Response:} We selected stakeholders in an effort to represent a range of disciplines. Although we did include patient advocacy experts in our process, we did not include actual patients with CKD. Other stakeholders such as nurses, social workers, and dietitians are also important stakeholders in CKD decisions and could be included in future efforts of this kind.
We have revised our discussion to reflect the potential limitation of our approach on page 12, paragraph 2: “Third, while our stakeholder group included representatives from two patient advocacy organizations, we did not include actual patients with CKD. Methods for selecting patients with appropriate levels of expertise (i.e., medical knowledge, awareness of issues affecting patients with CKD relevant to comparative effectiveness research) for this type of scientific effort are not yet well defined. Stakeholders’ input may also have been further enriched by our inclusion of non-physician medical professionals such as nurses, social workers and dietitians. Future efforts to identify topics for CER reviews should consider broadening stakeholder representation to include patients and non-physician medical professionals.”

Referee 1/Comment 4:

4) The prioritization process was to consider feasibility, but since the stakeholders expressed concern about the availability of literature to perform systematic reviews in several areas, topic prioritization proceeded without regard to feasibility. Subsequently, the research team performed a screen of pertinent literature for the top tiered topics. The authors then concluded that based on the number of available RCTS or cohort studies it appeared feasible that rigorous systematic reviews could be done. I would argue that rigorous systematic reviews can be done on any topic regardless of the yield, but that the value of information of such an exercise will depend on the number and quality of studies, how definitively they answer the question of interest, how this will reduce uncertainty or add to the current knowledge, and ultimately impact care. Recent existing systematic reviews and guidelines, as in the fields mentioned above, are likely to diminish the value added of de novo reviews, unless there is a reason to update them in order to include new, informative studies. Such a complex assessment will require more than simply counting of the number of publications in a preliminary literature screen. I believe the prioritized list is therefore more a reflection of what is considered to be important and ‘of interest’ in CKD care by the stakeholder panel, rather than a true blueprint for conduct of ‘high priority and potentially high value’ systematic reviews. To identify and refine ‘high priority and potentially high value’ topics for systematic reviews as well as primary CER research requires a coordinated effort that includes a standing professional forum with wide representation, a concerted and iterative needs assessment and methodological resources to refine concrete research questions. Decentralized and fragmented efforts, while allowing pluralism, come with the cost of unnecessary redundancy and inefficiency.

Authors’ Response: We agree with the reviewer that the conduct of value-added systematic reviews must be guided by more than just the availability of literature. We have revised our discussion on page 13, paragraph 2 to include considerations that should also guide the conduct of CER systematic reviews: “Also, while our preliminary findings suggest several topics may have enough evidence to make CER systematic reviews feasible, several factors determine whether a systematic review will add value to inform medical decision-makers, including the number and quality of studies available to review, how definitively identified studies answer the question of interest, and how answers to questions will reduce uncertainty or add to the current knowledge and ultimately impact care. These factors should all be considered prior to undertaking CER systematic reviews.”
Referee 1/Comment 5:

5) I saw with great interest the prioritization of less traditional systematic review topics, such as access to care, collaboration strategies, health information technology (which I think should emphasize decision support, rather than computer support), patient safety. These are innovative and cross-cutting themes, that hold great promise for improving CKD patient care, if they use a wider focus than only kidney outcomes. As shown in Table 3, these topics correspond to a small number of pre-existing systematic reviews and primary research studies. This seems to highlight a need for primary CER research.

Authors’ Response: We agree with the reviewer regarding the likely need for primary CER research in these areas. We have revised our discussion on page 12, paragraph 1 to now reflect this observation: “Other topics, such as studies evaluating the comparative effectiveness of health information technology and the study of collaborative care strategies (both ranked as ‘top tier’ by our stakeholders), represent novel areas of inquiry. We identified few studies of these topics during our feasibility assessment, potentially reflecting a potential need for primary CER studies in these areas.”

Referee 1/Comment 6:

6) Given the inherent complexities in stakeholder driven topic prioritization and the above limitations, I would like the authors to elaborate on lessons learnt or suggestions for strategies in research prioritization going forward to enhance the value of sharing their experience.

Authors’ Response: We appreciate the reviewer’s suggestion to broaden our recommendations for future efforts. We have now refined the final paragraph of our discussion to include our recommendations: “Future efforts such as ours might benefit from identification of an even more broadly defined group of stakeholders (e.g., patients and non-physician CKD health professionals), further refinement of protocols for engaging stakeholders throughout the topic identification process, and development of strategies for identifying areas in need of both CER systematic reviews as well as primary CER studies.”

Referee 1/Comment 7:

Minor Essential Revisions
Please add the final prioritized topic rank to the corresponding topics in Table 2 and the original topic number to Table 3 to allow cross referencing of topics, questions and ranks.

Authors’ Response: The topics in Table 2 are not listed in any particular order, but rather are simply grouped by domains (prevention, detection, progression and complications). Therefore, we have elected not to include corresponding topic numbers in Tables 2 and 3 as not to confuse the reader. To clarify this, we have included mention on page 9, paragraph 3 of the Results section that the topics in Table 2 are not listed in a particular order. We have also clarified this in the legend of the table itself:

Referee 2/Comment 1:
Can the authors define “community stakeholders” earlier in the manuscript? Did they include policy makers and clinicians only? More details could be provided, including justification as to why no patients with CKD were included.

Authors’ Response: We have revised the Introduction of our manuscript to better define “community stakeholders” on page 4, paragraph 3: “CER studies may be distinguished from other types of clinical research by their explicit goal of being highly responsive to priorities of community stakeholders (persons or groups who have a vested interest in a clinical decision and the evidence that supports that decision) who will use study findings to support their decisions about care.[11]” Our stakeholders included policy makers, insurers, clinicians, and research funders. They also included representatives from patient advocacy groups, but did not include actual patients with CKD, to our knowledge. Our lack of including patients stemmed, in part, from our difficulty identifying patients with appropriate expertise to adequately inform this type of research process. We have refined the discussion of the limitations of our project to include this consideration on page 12, paragraph 2:

“Third, while our stakeholder group included representatives from two patient advocacy organizations, we did not include actual patients with CKD. Currently, little guidance is available regarding the selection of patients with appropriate levels of expertise (i.e., medical knowledge, awareness of issues affecting patients with CKD relevant to comparative effectiveness research) to participate in efforts like this in a meaningful way. Fourth, our stakeholder input may have been further enriched by the inclusion of non-physician medical professionals such as nurses, social workers and dietitians. Future efforts to identify topics for CER reviews should consider broadening stakeholder representation to include patients and non-physician medical professionals.”

Referee 2/Comment 2:

Diversity in opinions among stakeholders was observed, one reason being that some were concerned about the paucity of evidence to compare existing strategies of care in certain topic areas (page 9). It would be interesting to understand the range of reasons underpinning the stakeholder decisions. For example, were the teleconferences recorded and transcribed, then analysed to identify reasons for identification and ranking of topics, or discussion around the overall rankings? Did the documents allow participants to make additional comments, which could also be analyzed?

Authors’ Response: We appreciate the reviewers’ thoughtful consideration of this issue. We did not transcribe our teleconferences with stakeholders. However, we did take careful notes on the process, and stakeholders did submit additional comments as part of the ranking process. While we did note these comments, we did not analyze them for themes, as we did not receive comments from all stakeholders in this format. We now mention this in our limitations on Page 12, paragraph 2: “Fifth, some stakeholders did submit additional comments in with their rankings, which provided additional context to their rankings. However, because all stakeholders did not comment to the same extent, we did not formally analyze these comments.”

Referee 2/Comment 3:
• More details on how the authors calculated summary scores/global rank is suggested.

Authors’ Response: We calculated summary scores based on the stakeholders’ ranking of their 10 highest priority topics (10 for highest, 1 for lowest). We allowed ties for overall rankings. We have added Appendix A, which describes our calculations in full detail.

Referee 2/Comment 4:
• The discussion could include how to make decisions about conducting CER systematic reviews in terms of rank and feasibility scores; do both carry equal weight?

Authors’ Response: We believe that both priority ranking and feasibility should be weighed when selecting topics for CER systematic reviews, and such reviews should only be conducted when they are expected to be high quality and value-added. We have revised our discussion to include a more in-depth discussion of the range of considerations we feel should influence the process of deciding whether CER reviews on topics should be undertaken on page 13, paragraph 2: “Also, while our preliminary findings suggest several topics may have enough evidence to make CER systematic reviews feasible, several factors determine whether a systematic review will add value to inform medical decision-makers, including the number and quality of studies available to review, how definitively identified studies answer the question of interest, and how answers to questions will reduce uncertainty or add to the current knowledge and ultimately impact care. These factors should all be considered prior to undertaking CER systematic reviews.”

Referee 2/Comment 5:
• Additional suggestions for future research could be stated including prioritization activities with patients diagnosed with CKD. Or, to assess and compare priorities between different groups of stakeholders including policy makers, funding agencies, clinicians, patients etc.

Authors’ Response: We have revised our Discussion to incorporate these considerations on page 13, paragraph 2: “Future projects of this kind may benefit from assessing and comparing independently determined priorities of different groups of stakeholders, including policy makers, funding agencies, clinicians, and patients.” and on page 14, paragraph 1: “Future efforts such as ours might benefit from identification of an even more broadly defined group of stakeholders (e.g., patients and non-physician CKD health professionals), further refinement of protocols for engaging stakeholders throughout the topic identification process, and development of strategies for identifying areas in need of both CER systematic reviews as well as primary CER studies.”

Referee 3/Comment 1:
1. This is an area of importance
2. The chosen methodology would seem reasonable and appropriate
3. The weaknesses in the methodology (notably the size of the stakeholder group, such that one topic made the final list on the basis of a single submission) are recognized and acknowledged
Specific:
Major Compulsory Revisions - None
Minor Essential Revisions
1. The authors should provide some justification of their decision to restrict the scope to patients with CKD 1-4

Authors’ Response: We have revised the manuscript to include further explanation for our decision to focus on the care of patients with CKD stages I-IV. On page 6, we now state, “From the outset, our team acknowledged the breadth of topics potentially relevant to the care of patients with CKD, ranging from studies of strategies to prevent CKD, to studies of strategies to prevent morbidity and mortality among patients with end stage renal disease (ESRD). We decided a priori to restrict our efforts to identifying priorities for CER reviews relevant to the care of patients with CKD stages I-IV because of time limitations (the process was funded to occur in less than 1 year) and differing considerations relevant to the care of patients with early or progressive CKD versus the care of patients with ESRD.”

Thank you for your consideration.

Sincerely,

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