Author’s response to reviews

Title: Criteria for assessing high-priority drug-drug interactions for clinical decision support in electronic health records

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Author’s response to reviews: see over
Dear Mr. Adrian Aldcroft,

Thank you for this opportunity to respond to the reviewer’s comments and resubmit our manuscript (Manuscript ID 1526840366789214) titled "Criteria for assessing high-priority drug-drug interactions for clinical decision support in electronic health records" to BMC Medical Informatics and Decision Making.

As noted previously, the associated paper on the set of high priority drug-drug interactions (DDI) identified using the criteria discussed in this paper has already been published by the Journal of the American Medical Informatics Association and we look forward to the publication of this work. In this paper, we describe criteria for assessing high-priority DDIs for clinical decision support in electronic health records. We are thankful to the reviewers for their encouraging remarks regarding the significance of this work and also recognizing the pragmatic approach undertaken to tackle the problem of insufficient information required in evaluating DDIs.

We are grateful for the suggestions provided by the reviewers and have incorporated these in the attached version of the manuscript. All the changes are detailed below and the revised version of the manuscript is attached. In the response to reviewers, page and line numbers are according to the revised version so as to enable the reviewer to easily see the changes made to the manuscript. Owing to the word count limit of the “Cover Letter” box, the responses to reviewers’ comments are detailed in the supplemental cover letter file.

Thank you once again for your consideration and for your valuable suggestions. We look forward to hearing from you.

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List of attachments:
1. Cover Letter with responses to reviewers’ comments
2. Revised manuscript with changes incorporated (Clean Copy) (incl. Figure Legend + Tables 1 & 2)
3. Figure 1: Search criteria used for identifying articles
4. Figure 2: Example of the virtual discussion among panelists
5. Additional File 1: List of relevant articles extracted for the systematic review
Methods:

Reviewer 1:

1.1. What were the key concepts or criteria used by the authors to select the articles? The search strategy itself seems broad (...). It would be helpful for readers to have a clearer understanding of the search strategy explained in the text.

The key concepts used in our search strategy are described in detail in Figure 1. In addition, we have described the methodology used on Page 5. On Page 5, Line 7, we describe the two categories of keywords needed in order to arrive at the list of articles that we were looking for.

“i) Category (A) consisted of terms that described a clinical information system or electronic medical record. A detailed list of keywords used in this category is listed in Figure 1.
   ii) Category (B) consisted of terms referring to medication-related decision support interventions including mechanisms (alerts, warnings, reminders, etc.) of generating MDS. A detailed list of keywords used in this category is listed in Figure 1.”

To clarify our search methodology, we have added the following sentences to the text on Page 5, Line 11. We identified a calculation error, in that we has 43 articles that matched our review criteria, we have incorporated this change as well.

“Using the keywords identified in categories A and B we identified 280,221 and 588 articles respectively. An intersection of these two sets of terms [A AND B] resulted in 192 articles which contained concepts from both sets of keywords. We reviewed the abstracts for these articles and identified 41 articles that matched our inclusion criteria. In addition, we looked at the bibliographies of “relevant articles”, which yielded 15 articles and a previously conducted systematic review on the topic of alert fatigue (van der Sijs, et al. 2006) identified 22 articles resulting in a total of 78 relevant articles. After removing duplicates, we had a total of 67 articles which were independently reviewed. Following a comprehensive review, of these articles, reviewers identified 43 articles that matched our criteria. Common reasons for excluding articles at this stage included: articles on e-prescribing and use of CPOE in various other clinical settings, use of CPOE in patient care management, treatment protocols / guidelines in relation to CDSS, disease management & Drug treatment comparisons, clinical drug trials & pharmacokinetic /pharmacodynamic studies, and cost effective analysis of treatment options.”

(...)

Authors should also note when I conducted a simple search in Medline with the same restrictions only on using ‘drug interaction’ (part of Concept B) as text and a Mesh term which resulted in > 15,000 articles.

Sure, however a combination of the sets of keywords for A AND B (as explained above) would result in a much smaller set of articles. In addition, the limits set for this search would further prune the results.
1.2. How were panel discussions structured and how was consensus on the 5 criteria and their priority achieved? If this is documented elsewhere, it should be briefly stated with a reference otherwise it would be helpful to include a paragraph on this process.

The following sentences were added on Page 7, Line 4 to explain how the panel discussions were conducted. In addition we have added Figure 2 to help the reader understand how the virtual discussions were conducted.

“In addition, we conducted individual phone calls with representatives from the three leading medication knowledge base (KB) vendors [Cerner Multum, First Databank, and Wolters Kluwer]. These phone calls provided in-depth discussion of the criteria identified via the literature review but also allowed discussion of practical considerations for the use of these criteria by knowledge base vendors in assessing DDIs. Additionally, the expert panel was provided the opportunity to discuss the criteria using an online portal called eRoom (EMC, version 7). An example of the discussion between expert panelists on the criteria of the ‘Evidence supporting the interaction’ is illustrated in Figure 2. Names associated with specific comments have been hidden to maintain the anonymity of the contributors.”

Results

2.1. Figure 1 What happened to the 23 articles that were removed before final review – was there a relevance problem? Perhaps there is some additional information missing from the diagram about how results were reviewed?

Please see Response to 1.1 above where we have clarified the search methodology. In addition, please see the text on Page 5, Line 11 where we have clarified the same in the manuscript.

2.2. Systematic Review results: (...) It is best practice when reporting reviews to provide the relevant articles as an appendix.

Please see Additional file 1 (Appendix A) where we have provided the relevant articles that were identified for this systematic review.

(...) and to quote significant articles to support the findings of the review in this case the five criteria for identifying clinically important drug-drug interactions. (...) annotating the Table 1 with relevant references to support their results.

We agree with the reviewer and have annotated the criteria listed in Table 1 with the relevant references. We chose to use seminal references for this annotation so for some criteria there may be more references from the ones used in the review than are listed in the Table.

A very important reference article would be ‘van Roon EN. Et al. 200. Clinical relevance (...), which describes the development of the drug interaction knowledgebase developed in the Netherlands (...).

Yes, this article is relevant and was part of our systematic review (Reference # 40) in the Additional File1.
2.3. Please clarify Headings in Table 1: The second column is headed definitions as posted in online discussion but it is difficult to understand what the dot points in this column contribute – rather than quoting ad hoc postings, it would be benefit the readers’ understanding and ensure that these criteria were applied in the future, if this information was brought together as a coherent summary for each criteria.

We have modified the headings in order to improve clarity and make these self explanatory. We disagree with the reviewer, the ‘dot points’ or bullets are not ad hoc postings but in fact sub-criteria from the expert panel discussion and the literature review. The format presented here will help the reader understand specific sub-criteria to be considered within each criterion.

2.4. It may be difficult for readers to understand the precedence of the items referred to in Table 2 barriers and considerations – I wonder if the reader may find it easy to understand if they were presented as two different tables ‘barriers’ and ‘considerations’.

The current format of table 2 provides the best readability in terms of barriers and considerations for each topic. I agree that the title of the column could be viewed as misleading. Therefore, we revised the title to demonstrate the precedence of the barriers then considerations.

2.5 Word missing - "Specificity of alerting can be improved by developing ......that take into account (assume the word is methods??)

Specificity of alerting can be improved by developing rules that take into account patient specific data.

Reviewer 3:
3. The handling of the interaction between aripiprazole and amiodarone is discussed on page 11. One of the suggestions is to replace amiodarone by a calcium channel blocker that does not inhibit the metabolism of aripiprazole (CYP3A4 mediated). Amiodarone is used for cardiac arrhythmia and replacing it by a calcium channel blocker is usually not feasible. Furthermore amiodarone has a long half life and the interaction may persist months after withdrawal. Monitoring of the plasma concentration of aripiprazole could also be recommended when used in combination with amiodarone.

Please see Page 10, Line 23 where we have made recommendations as suggested by the Reviewer and added a Reference for the suggested actions that can be taken if the two drugs are co-prescribed.

Discussion
Reviewer 3:

4. Some of the criteria specifically regarding clinical implications and patients characteristics are interesting and valuable but maybe not yet feasible to use. For example, scientific evidence on how to handle interactions and how they are altered by patient characteristics is unfortunately almost always lacking. This would make these criteria difficult to follow today but
hopefully there will be more information about this in 5-10 years. Please comment on this in the manuscript.

We have added this to the Discussion section on Page 15, Line 11.

Discretionary Revisions

Background

3. Reference 11 Page 4 Line 7 – does not appear to be correct?

Discussion

4. Reference 6, Page 17, Line 7 – is this correct?

5. The results and discussion would benefit from some abbreviation by limiting some of the examples and anecdotes and improving the paragraph structures.
Results and Discussion sections have been modified for brevity by limiting the examples and improving paragraph structures, as suggested by Reviewer1. We have retained the examples; we feel that these are important in helping the reader understand the relevant point being made.

6. The conclusion seems to miss out on bringing out the importance of national and international initiatives to assist with evaluating evidence for drug-drug interactions – as it had been mentioned in the discussion and maybe the only way we can ensure consistency across vendor in the future.
We revised the Conclusion on Page 17, Line 18 by stating that future research is still needed to develop standardized editorial guidelines and uniform adoption.

Reviewer 3

7. How was the literature search performed? Which exact Mesh terms/Emtree words were used? In figure 1 you specify all terms used but it is not clear if some of them were MeSH terms/Emtree terms or not.
Please see Response 1.1. Although we took into account concept represented as MeSH terms we when we were performing the search we did not document these separately and hence did not provide these in Figure 1.
Minor Essential Revisions

8. Page 11, correct the spelling of aripiprazole (line 5, 8, 10, 11)

We have corrected the spelling to “aripiprazole” on Page 10, Line 21 and Page 11, Lines 1, 4, 7, and 8.

9. Page 19, line 14, correct the spelling of itraconazole

The correct spelling of “itraconazole” has been updated on Page 16, Line 16.

10. How many criteria were identified by the literature search and how many of them were disregarded? Please comment on this in the manuscript.

We have added the following sentence on Page 8, Line 6 to identify the criteria that were identified from the literature search. No criteria identified from the literature search were disregarded.

“Twenty-four sub-criteria were identified for the 5 criteria: 4 for Severity of Interaction, 9 for Probability of Interaction, 3 for Clinical Implications, 5 for Patient characteristics, and 3 for Evidence Supporting the Interaction. We have listed these in Table 1 and identified the citation from which the sub-criteria were derived.”

11. The aim of the study, according to the abstract, is to identify a set of criteria for assessing the severity of DDIs. The criteria presented in the results are, to my opinion, not criteria for assessing the severity of DDIs but rather important criteria for how to choose which interactions to include in an EHR. Please specify what the specific purpose of the study is.

The reviewer is correct and we have amended the abstract and the manuscript to reflect the appropriate purpose of the study.

Also add in the discussion how these criteria should be used to improve drug-drug interaction warnings in electronic health care records.

We have modified the Discussion section to describe how these criteria should be used to improve DDI alerting in EHRs.

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