Reviewer's report

Title: Designing concept maps for a precise and objective description of pharmaceutical innovations

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Reviewer: Christine M Cheng

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Major Compulsory Revisions

Overall, I think this paper would be of interest mainly to informaticists and drug information specialists. However, I think the paper needs more focus on the process for how the concept maps were developed and tailored to physicians, with specific examples of challenging drugs, disagreements between the authors and processes to resolve disagreements.

• Methods
  o Subheading “choice of drug characteristics used to design the model”
  It would be helpful use a table or figure to list the drugs that were used to develop the concept maps, as well as the drugs that were used to validate the concept maps.
  o Subheading, “identifying information of interest to the physician,” first paragraph:
  Clarify how information of interest was selected. Was it solely by the authors? Or were physicians surveyed? If so, how were they surveyed? What was the response rate? What questions were they asked?
  o Subheading, “Modeling of pharmaceutical innovation,” sentence 5:
  Clarify the source of expert knowledge (authors, literature review, other sources).
  o Subheading, “Evaluation of the completeness of the model,” second sentence:
  Clarify – did all authors develop the concept map, then MI used the concept map for 40 drugs, and AV and CD verified MI’s work? Was there agreement/disagreement between AV, CD, MI on the elements of the concept map? Were there concepts that were eventually deleted from the original map?

• Results
  o Subheading “impact on safety,” sentence 5:
  Please define your criteria for “serious” drug interactions. Are these the clinically proven drug interactions vs interactions that are only theoretical or probable?
  o Bosentan example
  The example of bosentan dispersible tablets vs film coated tablets (comparing different dosage forms of the same drug) is a relatively weak example of the potential strength of the model. Perhaps authors could select a different
comparison, e.g., between different drugs used for the same indication (e.g., amiodarone vs dronedarone for atrial fibrillation, prasugrel vs clopidogrel, etc). It is not clear to me how this model would be used for drugs with multiple uses, e.g., prednisone, methotrexate, intravenous immune globulins. How does the model handle non-approved (off-label) uses?

- Discussion/Conclusion
  o Paragraph 2: Provide a reference for the statement, “In addition, concept map representation can be easily understood and used by nonmodeling specialists.
  o Comment on next steps to proving the value and utility of this model. Authors assert that this model can have wide utility, but have not proven that in this study.
  o The discussion/conclusion contains speculation on how useful the model is, which is not supported by the information presented in the article. The discussion and conclusion should instead focus on the limitations of the process for developing the model, and on next steps for validating the model among different potential users.

Minor Essential Revisions

- Reference #7 and figure #4 are not mentioned in the text.
- For electronic and online references, please note the date the reference was accessed.
- Conduct a spell check/grammar check. Do not capitalize generic drug names (bosentan and enoxaparin should not be capitalized).

Discretionary Revisions

- Background
  o This section is rather lengthy; authors could consider consolidating some of the background text (e.g., paragraphs 4-6 on drug approval reports from various agencies); alternatively, some of this information can be moved to the discussion section. Still another alternative is to describe in more detail the process and documentation available for new drugs in France.
  o Paragraph 8: In addition to describing the work of Carprino and Russo, authors may also consider including the Italian Medicines Agency criteria for ranking innovation of new drugs.
  o Last sentence, beginning with, “The results of our modeling…”: Consider removing or moving this sentence as it is more of a “methods” or “results” statement.
- Methods
  o Subheading “choice of drug characteristics used to design the model”
  Clarify why vaccines and diagnostic agents were excluded.
  o Subheading, “modeling of pharmaceutical innovation,” sentences 2,3:
  For readers who are not familiar with the layout of the evaluation report and the drug banks, clarify what information is found in the drug banks that is not in the
drug evaluation report or vice versa. Why did authors have to resort to consulting multiple resources instead of a single source? What information is each resource missing?

- Subheading, “Modeling of pharmaceutical innovation,” last sentence:
  Elaborate on how the drug monographs were evaluated for comparative safety (how did authors handle drugs that did not have direct comparison studies)?

- Subheading, “Evaluation of the completeness of the model,” first sentence:
  Sentence should read, “We used a random sample of 20 drugs taken from ….to validate the model.”

• Results

- Paragraph 2 (page 9):
  Does “new data” refer to post-marketing data? How is post-market data included? How frequently should a concept map for a drug be updated? Should it just be based on the drug label/review or should it also include non-manufacturer sponsored data?

- Subheading “modeling of the medical context of use of the new manufactured product,” sentence beginning with “Figure 2…”:
  Use “example” instead of “instantiation.”

- Subheading “impact on safety”:
  Authors may consider including that the safety/efficacy consequences of risks of overdose as well as underdose of a medication. This is particularly relevant for drugs with a narrow therapeutic index and that require therapeutic drug monitoring, e.g., serum drug level monitoring.

- Subheading, “impact on safety,” sentence 8 beginning with “Another important characteristic…”:
  Authors may consider including the availability of an antidote as a safety feature of a drug as well.

- Subheading, “impact on ease of use,” sentence 3:
  The example of enoxaparin is incomplete; clarify what drug enoxaparin is being compared to.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests