Author's response to reviews

Title: Evaluating Adverse Drug Event Reports in Administrative Data of Emergency Department Patients: A Validation Study

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Author's response to reviews: see over
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Re: Authors’ Response to Reviewers
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Title: Evaluating Adverse Drug Event Reports in Administrative Data of Emergency Department Patients: A Validation Study
Review 3

Dear Dr. Jones,

We have revised the manuscript according the reviewer’s comments, and have responded to their concerns below (in blue). We list the reviewer comments in the order of their appearance.

Thank you again on behalf of the investigative team, for providing us with an opportunity to revise and improve our manuscript.

We look forward to hearing from you again.

Sincerely,

Corinne Hohl
The case definition remains problematic and potentially misleading to readers; however, the acknowledgement in the Discussion section that the full case definition includes types of events that “may not be relevant from a pharmacovigilance or regulatory body perspective” such as “untreated indication,” “inappropriate dosing,” or “noncompliance” is recognized. Nonetheless, as the authors continue to include these broadly construed ADEs, they should at least clearly state the percentage of the total ADEs that involve these types of events. This percentage appears to be approximately 60-66% of the total ADEs in the study (from Table 3), which would be quite important to note.

We have added the breakdown of the categorization of all ADEs to the Results section in text (See Page 11, last paragraph).

However, it is hard for a reader to determine this precise percentage because of inconsistencies in terminology used in the discussion text, in Table 3, and Appendix B. Please apply the same terms consistently throughout.

We have harmonized the terminology throughout the manuscript.

Specifically:
- Is “inappropriate dosing” mentioned in the discussion inclusive of “high dose” and “low dose” mentioned in Table 3?
  Yes. We have edited the discussion section accordingly.
- Is “untreated indication” mentioned in the discussion the same as “drug use without indication” identified in the table or does it also include “need to add a drug”?
  No. “Untreated indication” is a synonym for the ADE type “Need to add drug/untreated indication” which is defined in Appendix B. In contrast, “drug use without indication” refers to the use of a drug without any medical indication for it. The latter is a drug that should be discontinued. We have harmonized the use of the terminology throughout the manuscript.
- “Need to add a drug” and “Untreated indication” are two separate categories in Table 3 but these two types are combined in Appendix B. Why?
  “Need to add a drug” and “untreated indication are in the same category in Table 3 and Appendix B. We have harmonized the use of the terminology throughout the manuscript.

The authors should add “need to add a drug” to the types of events enumerated in the discussion text that may not be relevant from a pharmacovigilance or regulatory body perspective.
- Should “wrong drug” also be considered an ADE that may not be relevant from a pharmacovigilence or regulatory body perspective?
  We have added “wrong drug” to the list of events unlikely relevant from a regulatory body/pharmacovigilance perspective.

2. In the Discussion, the authors assert that they "believe” that monitoring a broadly construed definition of ADEs “is desirable in order to guide the development and evaluation of evidence-informed health policies to reduce their occurrence” but do not explain how coming up with a composite, broadly construed ADE measurement would be useful to inform health policies or reduce occurrence. Please do so.

The examples given by the authors -- a patient with high CHADS2 scores that did not receive anticoagulation, a patient whose furosemide dose is reduced and then has pulmonary edema, and a patient who was non-compliant with insulin and went into DKA – may be issues of potentially
problematic health care (or may be the result of patient preferences or each may have its own web of complex causes), but the authors should explain specifically how labeling these disparate events “ADEs” is helpful for developing informed policies. Identifying frequency of occurrence of each situation individually would be important for prioritization.

Examining the underlying causes of each situation individually identify may guide specific prevention policies for anticoagulation, heart failure or diabetes management. But unless there is a common thread (e.g., lack of drug coverage led to the failure to use anticoagulants, led to lowering the dose of furosemide, and led to non-compliance with insulin) it is not obvious how lumping these situations under a common term, ADEs, helps inform prevention policies, unless it is a generic call that all health care providers should do a better job of high-quality prescribing and all patients should be more adherent to prescribed medication regimens.

Thank you for this comment. Please see our edits to pages 18 and 19 of the discussion in which we have elaborated on how collecting these types of data of disparate kinds of adverse drug events is presently may influence health policy. We have provided a specific example from the Vancouver Coastal Health Authority.

**Discretionary Revisions:**

3. Table 5 assesses the specificity of ICD code identification of ADEs (True Positive Cases identified by ICD codes / All True Positive Cases), but no mention is made of False Positives. The figures in tables 4 and 5 show the sensitivity, *i.e.*, the completeness of identification, and not the specificity.

Could a False Positive rate be calculated? The False Positive rate is particularly important for the broader ICD codes. For example, to identify the 62 of 221 ADE cases using the broader ICD codes, how many cases of the total cohort of were flagged by broad ICD codes as potentially having ADEs but did not by gold standard chart assessment. Did the ICD codes only identify these 62 cases or did they identify 500 of the 1574 patients (in this example 448 False Positives). If ICD codes were to be used to identify ADEs this would be very useful information and a high False Positive rate is further evidence that ICD coding may not be up to the task of identifying ADEs.

We have added the following text to the results section (see Results, pages 12 & 13) to describe the proportion of false positives, and the specificity of the code sets:

For the narrow code set: “This code set incorrectly identified 18 of 1353 records as false positive (1.3%; 95% CI 0.8-2.1%), corresponding to a specificity of 98.7% (95% CI 97.9-99.2%).”

For the broader code set: “This code set incorrectly identified 166 of 1353 records as false positive (12.3%; 95% CI 10.6-14.1%), corresponding to a specificity of 87.7% (95% CI 85.9-89.4%).”