Reviewer's report

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

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Reviewer: Daniel Budnitz

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- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

This manuscript has several fundamental concerns which must be addressed before a decision on publication can be reached.

First, the authors must re-phrase the title, abstract and text to indicate that they are attempting to identify “medication-related problems” (rather than adverse drug events) using ICD-10 administrative data. While there is some variation in definition of ADEs, the generally accepted definition is “an injury resulting from the use of a drug” which at minimum requires the presence of a drug (author’s ref 29 - Clarifying adverse drug events: a clinician’s guide to terminology, documentation, and reporting, Ann Intern Medicine). Four types of circumstances included by the authors (adverse drug reactions, drug interactions, drug use without indication, and high dose) are likely harms from use of the drug, and the authors should explicitly define each of these types of events. On the other hand, the other types of circumstances included by the authors -- low dose, need to add drug, noncompliance, and wrong drug -- may be related to low quality medical care but should not be considered “harm from use of a drug” (and if included also need explicit definition). If giving a “low dose” or needing to “add a drug” is considered an ADE, then every patient with hypertension who requires dose titration or addition of a second agent experiences multiple ADEs in the course of normal care. If “wrong drug” is an ADE, then every time empiric antibiotic therapy is changed based on culture and susceptibility results an ADE has occurred. The most obvious problematic circumstance identified by the authors and classified as an ADE is “noncompliance”. How can a drug which is not being taken by the patient be causing drug-induced patient harm? If the failure to take a drug is an ADE, then every asthma flare may be considered an ADE from inadequate treatment with anti-inflammatory medications. Indeed, in the authors' previous work they highlight a case in which a 27 year-old was non-compliant with their steroid inhaler and had an asthma flare as an ADE (cited as reference 21, although it appears that the authors do not have the correct title of the article – “Derivation of a Clinical Decision Rule to Identify Patients with Adverse Drug Events” looks like it should be “Clinical Decision Rules to Improve the Detection of Adverse Drug Events in Emergency Department Patients”) In summary, while all of these circumstances may involve failure of “ideal” medication use, they are not ADEs as generally understood by clinicians, drug
safety regulators, or most patient safety researchers. In fact, in a number of the author’s previous studies, the terminology “medication-related problems” (Ann Emerg Med. 2010;55(6):493-502) or “medication-related visits” (ref. 12) is used.

Second, a comparison of the data reported in this manuscript with data reported in a previously published article by the authors from what appears to be the same cohort of patients, from the same hospitals, over the same time period (reference 21) is difficult to reconcile. A slight difference in the total study cohort (1571 vs. 1591) might be explained by slightly different inclusion dates, however, the published article (cited throughout the methods section) identified 131 outcomes/ADEs while the current manuscript identified 221 outcomes/ADEs. From the method section of the manuscript which heavily cites reference 21, it appears that both studies use the same “criterion standard”, but is this truly the case? In addition to discrepancy in the total numbers of ADEs, data reported on the relationship to chief complaint and classification of types of ADEs in the published article (Table 2) and this manuscript (Table 3) are hard to correlate as well. This substantial discrepancy in assessment of the primary outcome of ADEs must be addressed by the authors. Are the cohorts completely different? If so the authors must clarify in the methods section. Are there substantial differences in the assessment of outcomes/ADEs between the two papers? In other words, are certain types of ADEs (e.g., “wrong drug” or “need to add a drug”) included in the “criterion standard assessment” of this manuscript but not included in the “criterion standard” in the previously published article? If the “criterion standard” for ADE identification is flexible, how can it be used as the basis for assessing validity of ICD codes for identifying ADEs?

Third, the authors say their objective is to determine the proportion of ADEs diagnosed at point-of-care that can be identified by ICD-10 coding. However, based on previous work by the authors, the treating clinician himself/herself did not recognize many instances to be ADEs, as defined by the authors, as such (Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Ann Emerg Med. 2010 Jun;55(6):493-502). How could administrative coding be expected to identify a clinical condition that the treating clinician himself/herself does not identify and document as such? The authors should show an analysis of the physician-diagnosed ADEs that were also identified using ICD-10 codes and not only the analysis based on external “criterion standard” determination after review by another physician or pharmacist to determine ADEs.

Fourth, code categories and C, D, E may be too insensitive to be useful. It is hard to determine, however, because the authors do not include a list of the ICD codes which they used. They do cite references which they state that they adapted; however, without a listing of the ICD codes used it is impossible to interpret analyses based on C, D, and E categories. Ideally the codes for categories A and B would be listed as well, but at least a reader could reproduce A and B categories from the description in the table, while it is impossible for the reader to guess how the authors might have chosen to select or adapt from references 26 and 27.
Fifth, the authors might have neglected key ICD-10 codes for "Drugs, medicaments and biological substances causing adverse effects in therapeutic us" (Y40-Y59). The Y codes are not listed in manuscript table 1, and are probably the absolutely most critical codes for identifying ADEs. The authors should explicitly stated that these codes are included. If they are not included this is a fundamental flaw in the analysis.

Finally, without a specific ICD code for non-compliance, assessing validity of ICD coding for identifying such events is unreasonable. To this reviewer’s knowledge, there is no ICD-10 code for non-compliance, but this should be stated by the authors in the manuscript. If there is a code for noncompliance, then the authors should explicitly identify it. Without a non-compliance code, it is virtually impossible for ICD codes to identify cases of non-compliance because the consequence of non-compliance is simply the progression of virtually any underlying disease condition (e.g., asthma, hypertension, skin infection, or even ACS if non-compliant with antiplatelet agent or cholesterol agent?).

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**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