Reviewer's report

Title: Estimating time-to-onset of adverse drug reactions from spontaneous reporting databases

Version: 2
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Reviewer: Stephen Evans

Reviewer's report:

General Comments (not numbered as they do not necessarily require a response)

This paper is generally clearly written and addresses an important point in relation to looking at times to occurrence of the reported onset of suspected adverse drug reactions (ADRs) in databases of spontaneous reports of such suspected ADRs.

As the authors say, there has been recent interest in looking at analysis of reported time-to-onset. The authors do not distinguish between different approaches used in the references they quote. One, at least, seems to deal with the data in a more appropriate way than the authors suggest.

There are also some questions of nomenclature. The authors do not seem to mention censoring and I think it is possible that in some instances what they suggest is truncation might also be right censoring.

I take truncation to mean that all the observations have a definite time to occurrence; the distribution is truncated by the fact that some times to onset may not be observed and be recorded in the database. It seems to me that this is true when all spontaneous reports are regarded as reflecting the observed time of occurrence. However, if we focus on a particular adverse event (let’s say lymphoma) reports of other events that are reported with, say anti-TNF# as the drug(s) of interest, being events for which the time to occurrence of lymphoma has been censored. They could be seen as being “at risk” of being reported with a lymphoma up to the time point at which the other (non-lymphoma) event occurs and is reported. Hence although the lymphoma event times are truncated, taking the non-lymphoma events into account allows for the median time to occurrence of lymphoma, and indeed the distribution of the time to the lymphoma. For signal detection purposes, it is likely to be the shape of the distribution rather than the mean or median itself, and the authors make reference to this.

Having said that, the approach taken by these authors is sensible and does allow for the obvious truncation.

It might be a different paper to see whether the bias in estimation of any of the parameters in actual databases (I suspect simulation will not necessarily help) is helped by paying attention to what might be seen as censored observations.
Other than this point this paper is original and very clear.

The only change might be to note that at least reference 20 (possibly also reference 19), in contrast to reference 18, does take a censoring approach which seems likely to have less bias than just taking observations that are in their entirety from a truncated distribution.

Answers to questions:

1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Yes
3. Are the data sound? Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes
6. Are limitations of the work clearly stated? Yes
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? Yes

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests

( I am an author of a paper referenced by the authors and also commented on in my review)