Reviewer’s report

Title: European Medicines Agency Policy 0070: an exploratory review of data utility in Clinical Study Reports for academic research

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Reviewer: Peter Doshi

Reviewer's report:

This paper does a few things. First, it provides a narrative review of how academics have used Clinical Study Reports, an enormously important but almost never used document type in academic research until the last 5-10 years. Second, the authors supplement a rich narrative account of the literature in this area with interviews from authors of the papers they describe to add additional depth. Finally, the authors speculate on the relative utility of the European Medicine Agency's landmark Policy 0070, which puts industry CSRs on the web (with virtually no barriers for public access).

This paper will be of interest to those working in this important and developing field, and I see no fundamental reason not to work towards publication.

I have some suggestions on how to strengthen the manuscript.

The abstract could make clearer, especially in the background section, that CSRs have been increasingly utilized over the past 5-10 years by academics doing systematic reviews and re-analysis of trials, mostly received through FOI requests or litigation. But there is an even more recent policy —Policy 0070— that will make obtaining CSRs for newer pharmaceuticals even easier. That is, without saying something like this, I found myself assuming - based on a read of the abstract - that the manuscript was going to be about how people have used CSRs released through Policy 0070. But in fact the manuscript is a speculation on the utility of Policy 0070 based on how CSRs NOT released through Policy 0070 have been used. This could be made clearer.

Also, throughout the manuscript, and starting on page 3, the authors refer to "selective outcome reporting". While this is absolutely a major concern that has been written about widely, it does not cover the misleading under-reporting of data, nor does it cover all types of misreporting, just one type (e.g. reporting secondary outcomes as primary). Therefore I feel the authors use of the term is sometimes (but not always) inaccurate and what they mean is more broadly "reporting bias", which includes publication and outcome reporting biases, but is not limited to these two. This is a bit of a fine point, but I think it should be corrected. In places (e.g. page 8, line 7), "selective outcome reporting bias" could be replaced by "misreporting" and I think it conveys what the authors actually mean.
Page 3, line 17-23. In this paragraph, I would add a few more important details regarding EMA's policy 0070. First, that it allows for global, public access to these documents for non-commercial purposes. Second, that the documents are available in PDF format, and do not include individual participant listings. It would also be good to note that Phase 2 - not yet implemented - aims to deal with the publication of participant level datasets. This is important as the "risk of re-identification" in Phase 1 refers to documents that are largely void of participant level data, even in narrative form.

Page 6, line 8: The authors may wish to update Tom Jefferson's presentation reference with this paper: http://dx.doi.org/10.1136/bmjebm-2018-110963 as it contains an updated version of this table. I believe this is currently ref 28.

Table 1. I would replace Jefferson reference with Cochrane review (which included zanamivir), or add additional citation to http://www.bmj.com/content/348/bmj.g2547 In addition I would add this Cochrane review as well as Eyding reference to the row on "Systematic review and meta-analysis".

Supplemental Table 1. Jefferson et al. didn't compare CSRs to trial manuscripts in ref 8. Comparing publications to CSRs was not part of our review. I would delete the italicized portion.

The authors use the phrase "manuscripts" instead of "journal publications" in various places in the manuscript. I found this a bit atypical and wonder if readers might think it is a reference to unpublished manuscripts. I think "journal publications" may be more readily understandable for readers.

Page 8, line 2. Typo in spelling of clinicalstudydatarequest.com

Ref #25 should have a URL.

Page 10 (end) and 11 (lines 1-4 and line 13 use of the word "aggregated"). I am slightly wary of the juxtapositioning the authors make between IPD and aggregate data, as they have implied that IPD is not in CSRs. This is not accurate as they know; CSRs do contain some patient level data, often enormous amounts. But what is disclosed under Policy 0070 is a separate question. This is a level of detail that I'm not sure is necessary to go into, and so I wonder if these paragraphs are necessary. Perhaps the authors can find another more straightforward way to explain to the reader about sources like CSDR for access to electronic patient-level datasets.


Appendix 1 misspells Jureidini's name in a few places.
Page 13, bottom. I am not sure it is true that newer CSRs do not contain individual AE listings and EMA isn't in possession of them. It may be true in some cases, but I do not think it is universally true and probably untrue in most cases. The authors should put a disclaimer like this after the quotation so that it does not read as the authoritative final word.

Page 14, top. This quotation is also problematic. It says that policy 0070 CSRs are "fully redacted". This is clearly untrue. Some sections are, but not the whole CSR which is clear from the rest of the quote. Needs fixing.

Page 16 (bottom half). The point is made that industry sometimes challenges the conclusions of academics who have reviewed their CSRs. I think the authors should, in addition to their suggestion for open dialogue between industry and academics, also recommend that transparency of the underlying data is an important aspect of ensuring a level playing field for those involved in a dispute, and for those who wish to take a look at the data for themselves, to form their own opinion.

Page 17, line 7. "rhetorical" is a bit unclear to me. Do you mean "speculative" or "inductive" or some such?

Page 17. But are patient narratives going to be available in Phase 2?

Page 17, line 22 "differ" not "different"

Page 17 line 27. Not true that narratives are out of scope for FDA's pilot. For example PDF p103 in https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/rev_210951_arn-509-003_CSR_Redacted.pdf

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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