Author’s response to reviews

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

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Author’s response to reviews:

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Dear Prof. Dirk Krüger (Editor)

Thank you for considering our manuscript entitled: “European Medicines Agency Policy 0070: an exploratory review of data utility in Clinical Study Reports for research.” We are delighted that BMC Medical Research Methodology has invited us to submit a revised version of our Research Article.

We would like to thank the reviewers for their time carefully reviewing our manuscript and for the positive and insightful comments made. We have responded to each comment made by the reviewers and revised the manuscript accordingly. Please find enclosed our authors’ responses,
marked-up copies of our materials with tracked changes and copied of our materials with these changes accepted.

We thank you again for your time and consideration of our manuscript and we look forward to receiving a final decision from BMC Medical Research Methodology.

Yours Sincerely

Dr. Sarah J Nevitt PhD
Research Associate in Biostatistics

BMRM-D-18-00596: European Medicines Agency Policy 0070: an exploratory review of data utility in Clinical Study Reports for academic research

Responses to reviewers

We would like to thank the reviewers for their time carefully reviewing our manuscript and for the positive and insightful comments made. Our responses are outlined below and changes made to the manuscript have also been highlighted in the text using tracked changes.

Jim Slattery (Reviewer 1):

This is a clear review based on opinions elicited from past users of CSR data. I have no substantive comments on the study.

Author response: Thank you for your positive comments on our review

Some wording could possibly be improved by a proof reader. For example on page 3 it may be better to say the policy 'came into effect' rather than 'has been effective' since the latter wording may be interpreted as a comment on its impact rather than its status.

Author response: Thank you, we have read through the manuscript again with a particular focus on the language and grammar

Peter Doshi (Reviewer 2):

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.

Author response: Thank you for your positive comments on our work

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.

Author response: Thank you for this comment, this is a good point.

We have reworded the background, objective, methods and conclusion of our abstract to clarify that the scope of this work was to review previous use of CSRs (prior to EMA Policy 0070) with the aim of hypothesising the data utility for future academic research of anonymised CSRs published under EMA Policy 0070.

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.

Author response: Thank you for this comment, another very good point.

We have reviewed all instances where we use the term ‘selective outcome reporting’ and edited to ‘misreporting or selective outcome reporting bias’ in two places where we do actually mean the two concepts (page 3, line 14 and page 8, line 8 of marked-up document).

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.

Author response: Thank you for the comment. We have added further details about EMA Policy 0070.

Page 3, line 17-20 of the marked-up document: “The European Medicines Agency (EMA) policy on the publication of clinical data for medicinal products for human use (EMA Policy 0070 ‘Phase 1’, herein referred to as EMA Policy 0070), allowing global access to regulatory documents for non-commercial purposes, came into effect January 2016.”

We have also further highlighted that the documentation is required to be published in anonymised PDF format (page 3, line 24 of marked-up document).

From our own experiences of regulatory CSRs and from reviewing the thirteen research reports within the present study, we have found that a lot of useful information related to individual participants can be found within the narrative sections. Therefore the risk of re-identification and data utility of these sections is of great interest (see additional text added to page 3, line 24-26 of marked-up document). Narratives are discussed further within the results and discussion section of the manuscript.

We completely agree with the reviewer that Phase 2 of the EMA Policy 0070 relating to the publication of IPD will bring additional challenges regarding risks of re-identification and data utility. Phase 2 is outside the scope of this work and to our knowledge at this time, there is no target date for the implementation of Phase 2. We have made reference to the planned Phase 2 of EMA Policy 0070 in our ‘Limitations and future considerations’ section (page 18 line 11-20 of marked-up document).

We prefer to restrict the details within the Introduction to Phase 1 only, with the additional suggestions of the reviewer for further details of EMA Policy 0070 Phase 1, so that the scope of this work is clear.

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.

Author response: Thank you, we have added the reference to the Jefferson 2018 paper.

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".
Author response: Thank you, we changed the Jefferson et al 2014 reference to the Cochrane review in Table 1 and throughout when making reference to the Jefferson et al review.

We have also added Eyding and Jefferson to the systematic reviews and meta-analysis row of the table. It was an oversight that the references were omitted from Table 1 (they are mentioned within Supplementary Table 1).

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.

Author response: Thank you for the additional insight, we have deleted ‘CSRs compared to trial manuscript.’

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.

Author response: Thank you, ‘Manuscripts’ updated to ‘publications’ throughout our manuscript and the supplementary material.

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

Author response: Thank you, corrected

Ref #25 should have a URL.

Author response: Thank you, URLs added for Clinical Study Data Request, YODA and also for the Kniola 2017 EMA presentation.

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.

Author response: Thank you for the comment. As the reviewer understands, we were not intending to imply that a complete individual participant dataset could be extracted from a CSR. Our intention was to describe differences between IPD reviews and systematic reviews which use aggregated data (whether published or unpublished).
We appreciate the perspective of the reviewer and understand how this paragraph could be confusing. Therefore we have deleted this paragraph and the section “Use of previously unpublished summary data for systematic reviews and meta-analyses” now begins “Previous work as shown that publically available information…”

Details of CSDR and YODA for requesting IPD are mentioned in the Discussion “Limitations and future considerations’ section (page 17, line 12).


Author response: Thank you, corrected

Appendix 1 misspells Jureidini’s name in a few places.

Author response: Thank you, corrected

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.

Author response: Thank you for the comment. We are quoting the words of the authors we interviewed. The quotations are clear and we have added further text to emphasise that this section is based on interviews and the quotes are the opinions of the authors. We have added a further note (page 14, line 4-6 of the marked-up document) that we have not verified the accuracy of the statements made by authors.

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.

Author response: Thank you for the comment and the insight. This is certainly an emotive topic which will provoke many opinions. We (the authors) have offered our opinion at the bottom of page 16 and we welcome the views of any readers of this paper on this topic.
Page 17, line 7. "rhetorical" is a bit unclear to me. Do you mean "speculative" or "inductive" or some such?

Author response: Thank you, we mean that we are hypothesising the impact of EMA Policy 0070 from our findings rather than based on direct use of CSRs anonymised under EMA Policy 0070. Certainty these interpretations are speculative too. Page 17, line 8 edited to ‘rhetorical and speculative.’

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

Author response: Thank you. We do not know the answer to this question. To the best of our knowledge at the time of writing, Phase 2 is still within the planning and scoping phase and extends to sharing IPD. Whether this also extends to listings of patient narratives, we are currently unsure, hence the uncertainty we express on page 17 (line 17-19) of the marked-up document.

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

Author response: Thank you, corrected

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

Author response: Thank you for the comment. Yes the reviewer is right that narratives relating to serious adverse events and deaths within the main body of the CSR are retained. We were referring to the ‘Subject Narratives’ (full listing). For example, see p101 of the FDA PDF, this attachment of Subject Narratives is not available.

We have clarified (page 17, line 26 of the marked-up document) that it is the full listings of participant narratives which are out of scope.