Author's response to reviews

Title: Reporting bias in medical research - a narrative review

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Author's response to reviews: see over
Dear Editorial Team, dear Referees,

Attached please find our point by point response to the referees’ suggestions, together with the revised manuscript and a document highlighting the changes made.

Best regards
Natalie McGauran

### Point by point response to referees

**Manuscript:**
Reporting bias in medical research - a narrative review (Natalie McGauran, Beate Wieseler, Julia Kreis, Yvonne-Beatrice Schüler, Heike Kölsch and Thomas Kaiser)

**Manuscript ID:**
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| **Referee 1 (Gowri Raman)** | **Authors’ response and amended text**  
* (amended text in italics; all changes indicated in the “TRACK CHANGES” document *) |
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<td><strong>Suggested revisions to the review</strong></td>
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In a further expert report, Dickersin noted “extensive evidence of reporting bias” [34], *which she further analysed in a recent publication with Vedula et al [90].* |
| 1-2 Pages 9-25: some of the sections describing specific drugs date back to issues from the 1980's. The review can be made more relevant by limiting to issues in reporting in the last 10 years. | We have deleted the example “prostaglandin analogues” (Lauritsen, 1987) in the text of the results section (now only included in Table 2). The other 2 examples from the 1980s are pivotal examples of reporting bias: (1) the first quantification of the overestimation of treatment effects (Simes, cancer therapy) and (2) the case that presumably caused most damage to patients (various authors, Class I anti-arrhythmic drugs). We would therefore prefer to leave these examples in the text. We have also removed an example published in 1990 (Chalmers, bed rest and ultrasound in pregnancy; now only included in Table 2). The vast majority of the remaining cases were published in the |
Page 27: Recent efforts to improve reporting of trials in clinicalTrials.gov are described in the following citations, suggest adding them:

Information and references added to page 27:
One of the first searchable computerized international registries of clinical trials was introduced in the United States in 1967; since then, several national and international trial registries have been created [154], such as the US government’s trial registry and results database ClinicalTrials.gov (see Tse et al for an update on this registry [155, 156]).

Reviewer 2 (Norma Terrin)

Minor essential revisions

There are concerns regarding the comprehensiveness of the review. As the authors state, “the review was based on the screening of full-text publications on reporting bias that had either been obtained by the Institute in the context of its HTA reports and other research work or were identified by the screening of the reference lists of the on-site publications.” This procedure should be justified, or addressed as a limitation, or a comprehensive search should be undertaken.

We have added a section on limitations of the review in the discussion section (page 26), which also addresses its comprehensiveness.

Limitations of the review

The review does not provide a complete overview of reporting bias in clinical research. Although our efforts to identify relevant literature went beyond the usual efforts applied in narrative reviews, the review is non-systematic and we emphasized this feature in the title. A substantial amount of relevant literature was available in-house and further relevant literature was obtained by screening reference lists. We dispensed with our initial plan to conduct a systematic review to identify cases of reporting bias, as we noticed that many cases were not identifiable by screening titles and abstracts of citations from bibliographic databases, but were “hidden” in the discussion sections of journal articles or mentioned in other sources such as newspapers, books, government reports or websites. As a search of bibliographic databases and the Internet using keywords related to reporting bias produces thousands of potentially relevant hits, we would therefore have had to obtain and read an excessive amount of full texts in order to ensure that we had not missed any
examples. This was not feasible due to resource limitations. However, within the framework of a previous publication [144] we had conducted a literature search in PubMed, and some of the citations retrieved formed the basis of our literature pool for the current review. In spite of this non-systematic approach, we were able to identify dozens of cases of reporting bias in numerous indications.

| 2-2 | There should be follow-up of the statement, “After the behaviour of Pfizer and Essex Pharma had been widely publicized, the companies provided the majority of study reports for the final HTA report, which will presumably be published at the end of 2009” | Updated information and reference included (page 11):

After the behaviour of Pfizer and Essex Pharma had been widely publicized, the companies provided the majority of study reports for the final HTA report. The preliminary report’s conclusion on the effects of mirtazapine was not affected by the additional data. For reboxetine, the analysis of the published and unpublished data changed the conclusion from “no statement possible” to “no benefit proven” [88]. |

| 2-3 | The funnel plot is not a valid diagnostic for publication bias, because publication bias is not the only potential source of funnel plot asymmetry. The asymmetry of the funnel plot in the magnesium meta-analysis could be the result of heterogeneity, since standard treatment for MI (the comparison treatment in the trials) changed over the years. The paragraph on magnesium should be deleted. | Paragraph on magnesium deleted in the results section (p. 14) and in Table 2. |

**Referee 3 (S. Nassir Ghaemi)**

| 3-1 | I think it is somewhat long and unevenly written. I suggest perhaps shortening the text if the table is to be kept as is. I also recommend removing the references to specific full names in the text in discussions of each paper. This will save space and also be more like standard academic style. | We have replaced the full names of authors with last names. In addition, following the suggestions by Referees 1 and 2 (Points 1-2 and 2-3), we have shortened the manuscript. |

| 3-2 | References to newspapers as sources, or tv shows, is unusual in scholarly journals. I think it is relevant though because this is a political issue, at one level, and those can be legitimate sources. However, I think they should be used judiciously and perhaps some discussion is needed of their likely validity. | We have added a section on limitations of the review in the discussion section, which also addresses the validity of the sources identified (page 27)

*Limitations of the review*

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Another potential limitation of the review is the validity of the sources describing cases of reporting bias. Although the majority of examples were identified in peer-reviewed journals, several cases were based on information from other sources such as newspaper articles and websites. However, we also regard these sources to be valuable as they provide a broader overview of reporting bias beyond well-known examples and also offer a starting point for more systematic research on the additional examples identified.

<table>
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<th>3-3</th>
<th>The introduction felt better written than the meat of the paper – the results. Perhaps more summarizing of the data, rather than a style of “this paper found this, that paper found that” would be better</th>
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<tr>
<td><strong>Additional changes by authors (see also“TRACK CHANGES” document)</strong></td>
<td>Due to the heterogeneity of the data and information, we do not think that summarizing the data would be feasible. In principle, the results section is therefore a collection of case reports. We hope that by shortening the text it has become more digestible.</td>
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| | **Influenza**

*Oseltamivir*

The BMJ and Channel 4 News reported on the difficulties in obtaining data for an updated Cochrane review on neuraminidase inhibitors in influenza [129]. A previous analysis of oseltamivir, which was used in the prior Cochrane review [130], was based on 10 industry-sponsored trials of which only 2 had been published in peer-reviewed journals [131]. The manufacturer Roche initially declined to provide the necessary data to reproduce the analysis and then only provided a selection of files [129]. The Cochrane authors (Jefferson et al) subsequently concluded that “Evidence on the effects of oseltamivir in complications from lower respiratory tract infections, reported in our 2006 Cochrane review, may be unreliable” [132]. Roche has since agreed to provide public access to study summaries and password-protected access to the full study reports [129].

| | Additional changes (see TRACK CHANGES document*):
- Permission from the Collaboration Collaboration to include Table 1 added
- Table 2 now included in the actual manuscript |
New example (Table 2)

| Influenza | Oseltamivir | Editorial on difficulties in obtaining data for a Cochrane review [129] | “Jefferson et al noted that the Kaiser analysis was funded by the drug’s manufacturer Roche and was based entirely on 10 trials funded by Roche, only two of which had been published as articles in peer reviewed journals…Jefferson et al asked for clarification from the authors, who directed them to Roche. After initially declining to provide the necessary data, staff at Roche sent the Cochrane reviewers a selection of files, which answered some questions but still left the reviewers unable to reconstruct the Kaiser dataset. Of particular concern, the eight unpublished trials, involving 2691 patients, included one of the biggest trials of oseltamivir. More worrying still, the academic author named on the trial’s abstract in the Kaiser analysis and in company documents has told the BMJ he was not involved in the trial” [129]. | [130-132] |