PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Reporting of Drug Trial Funding Sources and Author Financial Conflicts of Interest in Cochrane and non-Cochrane Meta-analyses: A Cross-sectional Study
AUTHORS	Turner, Kimberly; Carboni-Jiménez, Andrea; Benea, Carla; Elder, Katharine; Levis, Brooke; Boruff, Jill; Roseman, Michelle; Bero, Lisa; Lexchin, Joel; Turner, Erick; Benedetti, Andrea; Thombs, Brett

VERSION 1 – REVIEW

REVIEWER	Nicole Skoetz University Hospital of Cologne, Department I of Internal Medicine Germany
REVIEW RETURNED	13-Dec-2019

GENERAL COMMENTS	Thank you very much for revising the paper, all my comments are sufficiently answered

REVIEWER	Klaus Lieb Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Germany
REVIEW RETURNED	04-Jan-2020

GENERAL COMMENTS	This investigation of the extent to which Cochrane and non-Cochrane meta-analyses report trial funding, author-industry financial ties, and author-industry employment from included RCTs is timely and important for the field of transparency of COIs in drug research. The authors found that reported funding sources for some or all included trials was much higher in Cochrane compared to non-Cochrane meta-analyses as were trial author-industry financial ties and employment. They also showed that the reporting in Cochrane metaanalyses increased considerably compared to early metaanalyses in the year 2010. Major points: It is very likely that the requirements of Journals to report trial funding, author-industry financial ties etc of included RCTs decide to a large extent whether such ties are reported in the publication or not. Did the authors check the requirements of the respective journals to make clear whether the effect is a consequence of a lack of requirements or a shortcoming of the authors? The authors state that in 2012, the Cochrane Collaboration began to require that Cochrane reviews report trial funding sources and FCOIs of the primary researchers of all included trials in the characteristics of included studies table. It is likely that at least some protocols of Cochrane metaanalyses published in the years

	of 2016-2018 have been published before or close to 2012, i.e. the time of the new requirements. Did the authors see even higher reporting after exclusion of those metaanalyses with older protocols around 2012? Do the authors see any relationship of the extent of reported ties and the Cochrane Review group editing the published metaanalysis. It should at least be discussed that the engagement of certain editors may have contributed to the reporting. What does it mean that ties were reported „partial“. The reader should get an impression whether partial means e.g. „only mentioned for single RCTs in the discussion“ or „systematically for 90% of included RCTs“. Although information is given in eTable2, more summarizing information for the non-Cochrane metaanalyses should be given in the results section. Minor points: In the introduction, the seminal study by Bekelman et al., JAMA 2003 and its two updates by G. Schott et al. in 2010 could be cited. In their policy recommendations, authors could discuss that also other forms of COIs such as non-financial COIs might be worth reporting in the future, (see also Lieb et al., BMJ Open 2016). The authors mentioned that the selection of metaanalyses was representative of the spectrum of meta-analyses of drug interventions and the journals where they were published in 2016-2018. How was this proven?

REVIEWER	Ioana Cristea University of Pavia, Italy
REVIEW RETURNED	16-Jan-2020

GENERAL COMMENTS	The manuscript describes a carefully planned and thoroughly implemented and reported cross-sectional study of COI reporting for trials included in meta-analyses. The methods are sound and I have no substantial criticism. However, I was surprised that very little consideration seems to have been given to the quality of the meta-analyses (as for instance assessed with the AMSTAR), as well as to that of the included trials (for instance as risk of bias). For example, meta-analyses which did not include information about trial funding or author financial COI might have also been lacking in other aspects of how they were conducted or reported. Even if they weren't, this information might have been missing from the primary trials, particularly if these were older or poorly reported (hence the relevance of risk of bias). The authors did take the most recent eligible meta-analyses, but it is possible this would have also included older trials. The authors instead put a lot of weight on impact factor, for reasons that are not clear to me. Particularly the separation around the impact factor of the CDSR appears artificial, as there is very little proof impact factor is a proxy for anything in regards to the articles being published in the respective journals. If the authors had a hypothesis about the journal themselves, they should have looked more in depth to the policies of these journals and what they were requesting from authors. But if their interest is in the published articles (in this case meta-analyses), I am not sure how impact factor is related. What distinguishes the CDSR from other journals is probably related to the journal requirements and the way they are formulated and implemented, not impact factor.

	The oversampling of two journals (Medicine and to a lesser extent Plos One) is an important limitation to the generalizability of the findings. The authors transparently acknowledge this limitation, which is probably due of the study selection procedure.

VERSION 1 – AUTHOR RESPONSE

REVIEWER COMMENTS:

Reviewer #1:
1) Thank you very much for revising the paper, all my comments are sufficiently answered

We thank reviewer #1 for her careful review and comment on the manuscript in the previous round of reviews.

Reviewer # 2:

1) It is very likely that the requirements of Journals to report trial funding, author-industry financial ties etc of included RCTs decide to a large extent whether such ties are reported in the publication or not. Did the authors check the requirements of the respective journals to make clear whether the effect is a consequence of a lack of requirements or a shortcoming of the authors?

Although we did not systematically review journal websites to determine if journals had a policy to explicitly require that funding of trials included in meta-analysis be reported, we have never seen this in a journal's instructions to authors. Authors, reviewers, and editors follow guidance for reporting from the EQUATOR Network. PRISMA does not currently address reporting of funding sources and author conflicts of interest from trials included in systematic reviews and meta-analyses. Thus, we suspect that the low reporting in non-Cochrane reviews that we found is related to not having this requirement included in the PRISMA statement. To address this comment, we have expanded our discussion (Lines 365-374):

Most journals that specify reporting requirements stipulate that authors follow reporting standards for meta-analyses articulated in the PRISMA statement. The current version of the PRISMA statement does not address reporting of trial funding sources and FCOIs of trial authors by investigators who publish systematic reviews and meta-analyses.16,17 The forthcoming updated PRISMA statement, however, will require that trial funding, although not trial author FCOIs, be reported (personal communication, David Moher, May 22, 2019). Adoption and enforcement of the updated PRISMA reporting standards by journals could result in authors being better informed about the need for reporting funding sources and FCOI and in peer reviewers and journals being more likely to require transparent reporting.

2) The authors state that in 2012, the Cochrane Collaboration began to require that Cochrane reviews report trial funding sources and FCOIs of the primary researchers of all included trials in the characteristics of included studies table. It is likely that at least some protocols of Cochrane metaanalyses published in the years of 2016-2018 have been published before or close to 2012, i.e. the time of the new requirements. Did the authors see even higher reporting after exclusion of those metaanalyses with older protocols around 2012?

To address this comment, we edited the revised manuscript (Lines 357-362), "We did not examine whether performance differed by review groups or whether updated reviews based on initial protocols that pre-dated Cochrane's reporting policy may have been less likely to fully report. It is possible that reporting in Cochrane reviews could be improved even further by ensuring that all review groups are

fully compliant and that even reviews with older initial protocols report per Cochrane's current MECIR standards, as required by Cochrane.14"

3) Do the authors see any relationship of the extent of reported ties and the Cochrane Review group editing the published metaanalysis. It should at least be discussed that the engagement of certain editors may have contributed to the reporting.

We did not examine performance of individual Cochrane Review groups. There are currently 52 Cochrane review groups listed (https://www.cochranelibrary.com/about/cochrane-review-groups), and for the main outcome, there were 17 reviews that did not report. Thus, we did not attempt to evaluate on a group-by-group basis. To address this comment, as suggested by the reviewer, we have noted in the revised manuscript (Lines 357-362, "We did not examine whether performance differed by review groups or whether updated reviews based on initial protocols that pre-dated Cochrane's reporting policy may have been less likely to fully report. It is possible that reporting in Cochrane reviews could be improved even further by ensuring that all review groups are fully compliant and that even reviews with older initial protocols report per Cochrane's current MECIR standards, as required by Cochrane.14"

4) What does it mean that ties were reported „partial". The reader should get an impression whether partial means e.g. „only mentioned for single RCTs in the discussion" or „systematically for 90% of included RCTs". Although information is given in eTable2, more summarizing information for the non-Cochrane metaanalyses should be given in the results section

We thank reviewer #2 for pointing out that we had not clarified this. As now stated in the Methods (Lines 199-201), "For reporting of (1) trial funding sources, (2) trial author-industry financial ties, and (3) trial author-industry employment, meta-analyses were coded as (1) reporting for all included trials; (2) reporting for some, but not all, included trials (partial reporting); or (3) not reporting." We have also emphasized this by adding a note the first time we mention partial reporting in the results (Lines 296-297), "…reported, fully or partially (for some but not all trials)…"

Minor points:
1) In the introduction, the seminal study by Bekelman et al., JAMA 2003 and its two updates by G. Schott et al. in 2010 could be cited.

We have added the Bekelman et al. reference (reference #10).

2) In their policy recommendations, authors could discuss that also other forms of COIs such as non-financial COIs might be worth reporting in the future, (see also Lieb et al., BMJ Open 2016).

While non-financial interests can lead to bias, there is not consensus that systematic reviewers should try to report non-financial interests. Marc Rodwin, for example, has written on this topic and raised concern that definitions of non-financial interests as COIs blur the intended meaning of conflicts of interest, despite being possible sources of bias, and would be hard or impossible to define in contexts, such as summaries in reviews (e.g., Accountability in Research, 2017; BMJ, 2018). Quinn Grundy and colleagues (J Clin Epi, 2020) have documented the wide and inconsistent range of approaches to this. Consistent with this, the TACIT tool, which is being produced by Cochrane, focuses on funding and financial conflicts of interest. Since our study was entirely about reporting funding and financial conflicts of interest, since asking reviewers to try to report other interests is controversial, and since there is not an agreed upon method for doing this, we do not feel that we should comment on this.

3) The authors mentioned that the selection of metaanalyses was representative of the spectrum of meta-analyses of drug interventions and the journals where they were published in 2016-2018. How was this proven?

We have edited to further clarify that this was a consecutive sample of all eligible meta-analyses listed in PubMed during the study period (Lines 403-405, “However, the meta-analyses included in our study constituted a consecutive sample of the most recent meta-analyses listed in PubMed and, thus, represented all meta-analyses of drug interventions listed in PubMed during the study period.”

Reviewer #3:
1) The manuscript describes a carefully planned and thoroughly implemented and reported cross-sectional study of COI reporting for trials included in meta-analyses. The methods are sound and I have no substantial criticism.

We thank reviewer #3 for her emphasis on the methodological quality of our study.

2) However, I was surprised that very little consideration seems to have been given to the quality of the meta-analyses (as for instance assessed with the AMSTAR), as well as to that of the included trials (for instance as risk of bias). For example, meta-analyses which did not include information about trial funding or author financial COI might have also been lacking in other aspects of how they were conducted or reported. Even if they weren't, this information might have been missing from the primary trials, particularly if these were older or poorly reported (hence the relevance of risk of bias). The authors did take the most recent eligible meta-analyses, but it is possible this would have also included older trials.

We have addressed this comment in the study limitations (Lines 393-397, “First, we used impact factor as a rough proxy of the quality of the meta-analyses included, but journal impact factor is very much an imperfect proxy; it does not necessarily reflect the quality of the methods of the included meta-analyses. Rating meta-analysis quality in all included meta-analyses was beyond the scope of our study, given the resources that would have been required.”

3) The authors instead put a lot of weight on impact factor, for reasons that are not clear to me. Particularly the separation around the impact factor of the CDSR appears artificial, as there is very little proof impact factor is a proxy for anything in regards to the articles being published in the respective journals. If the authors had a hypothesis about the journal themselves, they should have looked more in depth to the policies of these journals and what they were requesting from authors. But if their interest is in the published articles (in this case meta-analyses), I am not sure how impact factor is related. What distinguishes the CDSR from other journals is probably related to the journal requirements and the way they are formulated and implemented, not impact factor

We have addressed this comment in the study limitations (Lines 393-397, “First, we used impact factor as a rough proxy of the quality of the meta-analyses included, but journal impact factor is very much an imperfect proxy; it does not necessarily reflect the quality of the methods of the included meta-analyses. Rating meta-analysis quality in all included meta-analyses was beyond the scope of our study, given the resources that would have been required.”

4) The oversampling of two journals (Medicine and to a lesser extent Plos One) is an important limitation to the generalizability of the findings. The authors transparently acknowledge this limitation, which is probably due of the study selection procedure

We agree with reviewer #3 that this is an important limitation and thank her for pointing it out.

VERSION 2 – REVIEW

REVIEWER	Klaus Lieb Department of Psychiatry and Psychotherapy, University Meidcal Center Mainz, Germany
REVIEW RETURNED	09-Feb-2020

GENERAL COMMENTS	Thanks for the revision. All my comments are sufficiently addressed.

REVIEWER	Ioana Cristea University of Pavia, Italy
REVIEW RETURNED	03-Mar-2020

GENERAL COMMENTS	The authors have responded to all my suggestions.