

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Evidence for Stratified Conflicts of Interest Policies in Research Contexts: A Methodological Review
AUTHORS	Graham, Scott; Karnes, Martha S.; Jensen, Jared T.; Sharma, Nandini; Barbour, Joshua B.; Majdik, Zoltan; Rousseau, Justin F.

VERSION 1 – REVIEW

REVIEWER	Joel Lexchin York University, School of Health Policy & Management
REVIEW RETURNED	21-Apr-2022

GENERAL COMMENTS	<p>This scoping review examined whether studies that on industry funding and author COI stratified these independent variables in determining their effect on four outcomes of interest: positive study results, evidence of methodological biases, study reporting quality, and results-conclusions concordance. The authors conclude that the current evidence does not support the stratification by type or magnitude common to existing policy or capture why such stratification might be important. Their position in light of their findings is that it is critical to “develop standardized taxonomies of industry funding and/or author COI. These taxonomies combined with magnitudes allow for computation and aggregation of COIs essential for supporting rigorous research to guide COI policies in research contexts.”</p> <p>As someone who has done extensive research on COI I entirely agree with the authors that this has profound effects on the outcomes of research. However, beyond policies that prohibit certain types of COI is there any evidence that COI policies actually affect the quality of research, i.e., does having a policy make research better. It seems to me that this is the basic question that we need to answer.</p> <p>It's not clear to me what aspects of the relationship between trial authors and companies the term “employment” refers to. Does it just mean being an employee of a company or does it also include being on a speakers’ bureau? Similarly, the term “consulting” needs to be defined. Finally, how was industry funding defined, e.g., was the provision of the study drug or data analysis by the company considered industry funding?</p> <p>I also have a few other minor points:</p> <ol style="list-style-type: none">1. Page 3, line 5: There is something missing between “review” and “the”.2. Page 4, line 28: There is something missing between “though”
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	<p>and “overarching”.</p> <p>3. Page 4, lines 44-56: It should be made clear that these various scorecards evaluate the presence or absence of policies and if the policies are present their strength. These scorecards do not look at the effect of policies on the outcomes of research.</p> <p>4. Page 7, line 53: Why were biologics not considered drugs?</p>
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REVIEWER	Quinn Grundy University of Toronto, Lawrence S Bloomberg Faculty of Nursing
REVIEW RETURNED	02-May-2022

GENERAL COMMENTS	<p>Thank you for the opportunity to review this manuscript, which details a scoping review of studies that quantitatively assessed the relationships between industry sponsorship of clinical trials of drugs or medical devices and/or author conflict of interest and outcomes of interest including favorability of trial results (for the sponsor), methodological biases, reporting quality, and concordance between results and conclusions.</p> <p>This review, which I think may be better described as a methodological review rather than a scoping review, contains important methodological insights for studying the effects of industry sponsorship and author COI as well as important policy insights for developing funding and COI policy that mitigate risks to research integrity.</p> <p>In general, I think the study could be strengthened by clarifying the reporting, particularly in the Methods and the Results. While the authors focus on clinical trials and policies at academic medical centres, I think the results and the review’s impacts could be strengthened by making reference to other funding/COI policies related to biomedical research. For example, the focus on academic medical centres brings a strong physician focus to the research and is but one setting for biomedical research. Reference to stratified policies by journals, funders, or bodies such as the National Academies might be made in the Introduction and Discussion to contextualize the results related to clinical trials and AMCs.</p> <p>Major comments: I must admit that it took me several pages to really appreciate what was meant by ‘stratification’ in the manuscript’s title, abstract, and Introduction. I would suggest more thoroughly defining and describing the idea of “stratification” in the context of COI policies. The authors conclude that there is little evidence for stratification and I wonder if partly, this is because it is difficult to pin down conceptually (the authors describe the many ways industry sponsor or financial relationships with industry that create COI can be stratified). It would be helpful to have this conceptual clarity in the abstract and in the introduction.</p> <p>This conceptual clarity was also missing for me in the Methods. On page 7, under “Data Extraction and Synthesis,” I did not understand the distinctions between “stratified,” “unstratified,” or “magnitude” or the other subcategories. The information in the Supplementary Table was helpful, but I really needed this information also in the Introduction/Methods sections. Then, in the Results section, the terminology related to stratification shifted and introduced further confusion. For example, on line 47, p 8, the authors refer to “funding magnitude stratifications.”</p>
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	<p>The authors have chosen a scoping review design. However, because they are updating a systematic review, it is unclear why they have chosen to perform a scoping review, which is a distinct methodology. The review would be strengthened if the authors provided a rationale for why a scoping review best addresses. In terms of methodology, this struck me as more akin to what are termed “methodological reviews” rather a scoping review (see 10.1080/1364557032000119616 and related updates), which typically aims for a more exploratory approach or to synthesize heterogeneous or distinct bodies of literature. Clarifying the approach would be helpful in demonstrating or strengthening the congruence between the research question/aim, approach to the search, data extraction, and synthesis.</p> <p>In the Methods, I did not fully understand the phases of the scoping review nor the relationship with the previous systematic review the authors reference – it would be helpful to clarify which aspects replicated the previous protocol. It also took me some time to realize the previous systematic review was the Cochrane review on the topic and not work conducted by this author team. Given the rigour associated with Cochrane systematic review methodologies, I would highlight that you replicated another team’s Cochrane search strategy. Then, it would be helpful if the specific aims of the current review were clarified including what is meant by “evaluating different types of industry funding or author COI on target outcomes in biomedical research” and “focused at greater level of granularity on the specific operationalization of variables.”</p> <p>I found the Results section confusing at times and would suggest some reorganization of the reporting to really clarify what was found and its significance. Some of it also feels like it is written in a bit of a shorthand, which may be intelligible for those working in this area, but might miss a slightly wider audience. For example, under Industry Funding and COI IV types, it would be helpful to first consider the findings related to industry sponsorship and then separately, the findings related to author COI. The distinction is important and I think needs to be pulled out throughout – for a non-specialist audience, you might consider really explaining why these would be treated differently. Similarly, in referring to outcomes evaluation, references to “favorability of outcomes,” for example, should also include the explanation that they are “favorable to the sponsor.”</p> <p>Throughout, I think the key findings could be made more explicit. For example, to me, key findings that should be emphasized included: ‘isolated assessments of author COI did not show up until 2005,’ and “The favorability of outcomes [to the sponsor] has long been the dominant focus. . .”</p> <p>The Results section could also be enhanced by including some illustrative examples from studies that did stratify their analyses in different ways. In the section on Industry Funding and COI stratification, it would be helpful to have separate paragraphs for the different ways that analyses could be stratified and illustrative examples of each and then, key findings from included studies. For example, how did they assess COI strata by disclosure practices versus COI type?</p> <p>Finally, in the Discussion and Abstract, the authors emphasize that there is no evidentiary basis for stratified COI policies, but I would</p>
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	<p>strongly suggest clarifying throughout that this is an argument for developing this evidence (which would be a clear outcome of a methodological review) rather than undermining or withdrawing COI policies for which this evidence does not exist. At times, it was not clear whether the 'lack of evidence' was due to the absence of evidence or the existence of contradictory evidence. Overall, the rationale for having evidence-based COI policy could be strengthened.</p> <p>Minor comments: Removing all acronyms except maybe COI, would enhance readability (e.g. IV/DV).</p> <p>Abstract: - Per my comments above, it would be helpful to define 'stratified' COI policies</p> <p>- The header "search strategy" should perhaps read "Methods"</p> <p>- The authors reference "funder relationship to product" – unclear what product refers to here</p> <p>- Specify in the conclusion whether this statement "but these policies may not be well grounded in evidence" is due to absence of evidence or contradictory evidence</p> <p>Introduction</p> <p>- It would be very useful to define COI in this context and that the focus is author COI arising from financial relationships with medically-related industry (with an interest in the outcome of the research) (if I read this correctly)</p> <p>- Perhaps note the comparison group: "Available evidence indicates that industry-funded trials can be up to 5.4 times more likely to return positive results,[8] and trials with author COI may be as much as 8.4 times more likely to return favorable results.[6]"</p> <p>- Specify nature of effects, i.e "measurable [adverse] effects on biomedical research"</p> <p>- It would be helpful to define what "efficacy" means in the context of a COI policy – how would this be indicated/measured?</p> <p>- What is meant by "Competing guidelines for stratified COI policy"? The language is a bit confusing given the common use of 'competing interests' as a name for these kinds of policies.</p> <p>- Pg 2. Is there a more elegant way to state "the holder of the relationship"?</p> <p>- It would be interesting to see an example of: "They do not always agree on the severity of different COI." (pg. 2) The US DHHS example is not particularly illustrative as it is a threshold for disclosure not an acceptable/prohibited COI.</p> <p>- I did not understand this sentence: "The substantial investments in establishing differential policies involve stratifying the risk to the research enterprise based on COI type and magnitude." What are the substantial investments referring to?</p>
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	<p>Methods</p> <ul style="list-style-type: none"> - The tense seems to shift a bit and the sections written in active voice/first person were much more readable. <p>Results</p> <ul style="list-style-type: none"> - line 3, pg 8, do you mean that 35 studies considered industry sponsorship of the study and author COI with a company to be the same phenomenon? You then state that “isolated assessments of author COI did not show up until 2005”. These points seem to belong together and perhaps require a bit more explanation in the text as this may be a key methodological finding/consideration. - line 40, pg 10, what is meant by ‘funding disclosure practices’ in: “Relationships between COI or funding disclosure practices and outcomes of interest.” Does this refer to ‘actual’ versus ‘reported’ COI? I find this a difficult distinction because apart from Open Payments or other industry sources of data on financial relationships, nearly all COI data is ‘reported’. - I think Table 2 could be more impactful if it was organized by DV Type rather than study. Then, readers could compare the body of findings more easily. <p>Discussion/Conclusion</p> <ul style="list-style-type: none"> - Given that the Cochrane review provided rigorous and unambiguous evidence about the relationship between industry sponsorship and research outcomes, I was surprised that an additional 92 articles were identified that were published since 2016. I wonder if the authors might comment on this? - “The common treatment of COI as an undifferentiated category of industry funding compromises the ability to meaningfully discriminate between the potential effects of industry funding or author COI.” Yes! I think this is such an important point. If the authors reframe this as a methodological review, I think these key points can be made more of and are the real contribution of this review. - The authors make important policy recommendations, but I might suggest that these be moved and further developed in the Discussion rather than in the Conclusion. - I may have missed it, but I did not feel this statement was supported by the Results: “the results of this scoping review further support recent recommendations for attention to institutional COI at AMCs.” - The authors suggest that COI policies at AMCs may be predominantly informed by risks to clinical practice and medical education rather than biomedical research. While I agree, I think this is in part due to the core functions of AMCs and the fact that other institutions have COI policies related biomedical research that also cover these clinician scientists (e.g. funders, journals etc). I think this point needs to be addressed in both the Introduction and the Discussion and the focus on AMC policies either expanded or justified.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: This scoping review examined whether studies that on industry funding and author COI stratified these independent variables in determining their effect on four outcomes of interest: positive study results, evidence of methodological biases, study reporting quality, and results-conclusions concordance. The authors conclude that the current evidence does not support the stratification by type or magnitude common to existing policy or capture why such stratification might be important. Their position in light of their findings is that it is critical to “develop standardized taxonomies of industry funding and/or author COI. These taxonomies combined with magnitudes allow for computation and aggregation of COIs essential for supporting rigorous research to guide COI policies in research contexts.” As someone who has done extensive research on COI I entirely agree with the authors that this has profound effects on the outcomes of research. However, beyond policies that prohibit certain types of COI is there any evidence that COI policies actually affect the quality of research, i.e., does having a policy make research better. It seems to me that this is the basic question that we need to answer.

Response: Thank you for this encouragement. We have revised the introduction and discussion to highlight this essential question and the contributions this work can make to it. We agree that it is essential to determine if COI policies have any impact on the quality of research. We also think that it is unlikely that COI policies will have any effect if they are not grounded in the best available evidence. The need for evidence is especially acute for stratified COI given that level of detail in policy guidelines is inverse to the amount of evidence available to ground the policy. Specifically, we have added this sentence to the background “If one were to assess the efficacy of COI policies (i.e., determine if COI policies have any effects on the quality of research), one must first assess whether policies stratified by COI types are grounded in evidence about the differential risks of different COI types” (p. 6).

Comment 2: It's not clear to me what aspects of the relationship between trial authors and companies the term “employment” refers to. Does it just mean being an employee of a company or does it also include being on a speakers' bureau? Similarly, the term “consulting” needs to be defined. Finally, how was industry funding defined, e.g., was the provision of the study drug or data analysis by the company considered industry funding?

Response: Thank you for highlighting the need to clarify these issues. We revised to emphasize that these terms are used in inconsistent ways throughout the literature. In particular, the new Industry Funding Variable Assessment (pg. 10) and COI Variable Assessment (p. 12) sections each provide an illustrative range of definitional approaches to funding and COI. We have also added an additional note to the discussion to indicate how the inconsistency in funding and COI definitions stymies research in these areas and demonstrates the need for developing standardized taxonomies (pp. 15-16).

Minor comments: (Responses in parentheses)

1. Page 3, line 5: There is something missing between “review” and “the”. (This sentence was deleted in revision.)
2. Page 4, line 28: There is something missing between “though” and “overarching”. (This sentence was also deleted in revision.)
3. Page 4, lines 44-56: It should be made clear that these various scorecards evaluate the presence or absence of policies and if the policies are present their strength. These scorecards do not look at the effect of policies on the outcomes of research. (Thank you for this point. It was not our intent to imply otherwise, and we have now edited the relevant section (first paragraph of page 6) to ensure that we clearly describe how these studies are conducted.)

4. Page 7, line 53: Why were biologics not considered drugs? (This exclusion was included in error and has been removed. Thank you for catching it. Studies related to biologics are included in the dataset.)

Reviewer: 2

Comment 1: This review, which I think may be better described as a methodological review rather than a scoping review, contains important methodological insights for studying the effects of industry sponsorship and author COI as well as important policy insights for developing funding and COI policy that mitigate risks to research integrity.

Response: We agree, and we thank you for the suggestion. We have comprehensively redefined our approach as a “methodological review” and framed it as such throughout the manuscript.

Comment 2: In general, I think the study could be strengthened by clarifying the reporting, particularly in the Methods and the Results. While the authors focus on clinical trials and policies at academic medical centres, I think the results and the review’s impacts could be strengthened by making reference to other funding/COI policies related to biomedical research. For example, the focus on academic medical centres brings a strong physician focus to the research and is but one setting for biomedical research. Reference to stratified policies by journals, funders, or bodies such as the National Academies might be made in the Introduction and Discussion to contextualize the results related to clinical trials and AMCs.

Response: Thank you also for these suggestions. We have now clarified throughout the manuscript as recommended. We emphasize that the study was designed to apply broadly to biomedical research institutions including, but not limited to AMCs. In the discussion, in particular, we now indicate which findings are specific to AMCs and which should be considered more broadly applicable.

Comment 3: I must admit that it took me several pages to really appreciate what was meant by ‘stratification’ in the manuscript’s title, abstract, and Introduction. I would suggest more thoroughly defining and describing the idea of “stratification” in the context of COI policies. The authors conclude that there is little evidence for stratification and I wonder if partly, this is because it is difficult to pin down conceptually (the authors describe the many ways industry sponsor or financial relationships with industry that create COI can be stratified). It would be helpful to have this conceptual clarity in the abstract and in the introduction. This conceptual clarity was also missing for me in the Methods. On page 7, under “Data Extraction and Synthesis,” I did not understand the distinctions between “stratified,” “unstratified,” or “magnitude” or the other subcategories. The information in the Supplementary Table was helpful, but I really needed this information also in the Introduction/Methods sections. Then, in the Results section, the terminology related to stratification shifted and introduced further confusion. For example, on line 47, p 8, the authors refer to “funding magnitude stratifications.”

Response: We have revised the abstract, introduction, and methods section to further clarify what is meant by “stratification” from the very beginning. See p.1- new parentheticals in methods section of abstract; p.3-4 formal definition of stratification types with parenthetical examples; and p. 9- enhanced description of data extraction methods, with particular attention to defining COI variable types. We believe the new sections on stratification are further supported by the shift in language to a “methodological review” which helps focus attention on our analysis of variable design and definition.

Comment 4: The authors have chosen a scoping review design. However, because they are updating a systematic review, it is unclear why they have chosen to perform a scoping review, which is a distinct methodology. The review would be strengthened if the authors provided a rationale for why a scoping review best addresses In terms of methodology, this struck me as more akin to what are termed “methodological reviews” rather a scoping review (see 10.1080/1364557032000119616 and related updates), which typically aims for a more exploratory approach or to synthesize heterogeneous or distinct bodies of literature. Clarifying the approach would be helpful in demonstrating or strengthening the congruence between the research question/aim, approach to the search, data extraction, and synthesis.

Response: We agree and have changed the description of the design from scoping review to methodological review throughout. Thank you for this suggestion.

Comment 5: In the Methods, I did not fully understand the phases of the scoping review nor the relationship with the previous systematic review the authors reference – it would be helpful to clarify which aspects replicated the previous protocol. It also took me some time to realize the previous systematic review was the Cochrane review on the topic and not work conducted by this author team. Given the rigour associated with Cochrane systematic review methodologies, I would highlight that you replicated another team’s Cochrane search strategy. Then, it would be helpful if the specific aims of the current review were clarified including what is meant by “evaluating different types of industry funding or author COI on target outcomes in biomedical research” and “focused at greater level of granularity on the specific operationalization of variables.”

Response: Thank you for this suggestion. We have comprehensively rewritten the first paragraph of the methods section (p. 7). In addition to redescribing our approach as a methodological review, we take more time to clarify that we have replicated the search strategy and inclusion criteria from the preexisting Cochrane review and subsequently conducted a novel methodological review of the collected articles.

Comment 6: I found the Results section confusing at times and would suggest some reorganization of the reporting to really clarify what was found and its significance. Some of it also feels like it is written in a bit of a shorthand, which may be intelligible for those working in this area, but might miss a slightly wider audience. For example, under Industry Funding and COI IV types, it would be helpful to first consider the findings related to industry sponsorship and then separately, the findings related to author COI. The distinction is important and I think needs to be pulled out throughout – for a non-specialist audience, you might consider really explaining why these would be treated differently. Similarly, in referring to outcomes evaluation, references to “favorability of outcomes,” for example, should also include the explanation that they are “favorable to the sponsor.”

Response: We have reorganized the results section per these recommendations. Specifically, we now have designated sections for Industry Funding Variable Analysis (pp. 10-11), COI Variable Analysis (pp. 12-14), and Target Outcomes Analysis (p. 14). Each of these sections combine the available data and evidence synthesis to provide a more comprehensive analysis of each variable type. Specifically, each section now provides the overarching descriptive statistics for the variable type, illustrative examples of variable operationalization and use, as well as secondary analyses appropriate to each variable type. We have also further clarified that “favorability” is “favorability for industry” in the outcomes section and throughout the manuscript.

Comment 7: Throughout, I think the key findings could be made more explicit. For example, to me, key findings that should be emphasized included: “isolated assessments of author COI did not show up until 2005,” and “The favorability of outcomes [to the sponsor] has long been the dominant focus. . .”

Response: We have added a new paragraph to the beginning of the Discussion section (p. 15) that emphasizes the key findings in the context of the introduction. We have also relocated the 2005 datapoint to the top of the new COI Variable Assessment section to highlight its importance (p. 12).

Comment 8: The Results section could also be enhanced by including some illustrative examples from studies that did stratify their analyzes in different ways. In the section on Industry Funding and COI stratification, it would be helpful to have separate paragraphs for the different ways that analyses could be stratified and illustrative examples of each and then, key findings from included studies. For example, how did they assess COI strata by disclosure practices versus COI type?

Response: The reorganization of the larger Results section accomplishes this and has the advantage of adding only minimal additional text. Specifically, the previous submission had representative examples in the stratification section. These are now included in the Industry Funding Variable Assessment (p. 10) and COI Variable Assessment (p. 12) sections thus assuring that illustrative examples are closer to the original description of findings. We have also provided an illustrative description of the range of approaches to variable definition in each section that we believe will serve to further clarify these points.

Comment 9: Finally, in the Discussion and Abstract, the authors emphasize that there is no evidentiary basis for stratified COI policies, but I would strongly suggest clarifying throughout that this is an argument for developing this evidence (which would be a clear outcome of a methodological review) rather than undermining or withdrawing COI policies for which this evidence does not exist. At times, it was not clear whether the 'lack of evidence' was due to the absence of evidence or the existence of contradictory evidence. Overall, the rationale for having evidence-based COI policy could be strengthened.

Response: Thank you for this key insight that our results could be read in this way. We concur that the findings point to the need to develop this evidence: an idea we needed to make explicit. We have edited the abstract and discussion to offer a clearer account of what our study findings do and do not suggest. Specifically, we now indicate throughout that our findings demonstrate the need for new research designed to guide the construction of COI policies in research contexts. We have also added a new section to the conclusion that very specifically indicates we not calling for a suspension of COI policies, but rather that research should not continue to re-document a well-established finding (p. 18). Instead, we argue that the overall methodological review shows that research on COI has become narrow in study design and needs to be expanded.

Minor comments: (Responses in parenthesis)

Removing all acronyms except maybe COI, would enhance readability (e.g. IV/DV). (All acronyms have been removed except COI and AMC.)

Abstract:

- Per my comments above, it would be helpful to define 'stratified' COI policies. (This is now clarified by parenthetical in the abstract.)

- The header "search strategy" should perhaps read "Methods" (This is now corrected.)

- The authors reference "funder relationship to product" – unclear what product refers to here. (This refers to the difference between research sponsors who manufacture the product being evaluated and

sponsors who manufacture a competitive product. The distinction has been clarified by parenthetical in the abstract, results, p. 1.)

- Specify in the conclusion whether this statement “but these policies may not be well grounded in evidence” is due to absence of evidence or contradictory evidence

Introduction. (We now clarify the specific issue, i.e., “this review shows that the available research has generally not been designed to assess the differential risks of COI types or magnitudes. Targeted research is necessary to establish an evidence base that can effectively inform policy.” P.1. We also note in the manuscript conclusion, “Although substantial evidence exists that industry funding and COI have adverse effects on biomedical research, the current evidence cannot guide policy stratification by type or magnitude.” p. 18)

- It would be very useful to define COI in this context and that the focus is author COI arising from financial relationships with medically-related industry (with an interest in the outcome of the research) (if I read this correctly) (We are unable to add additional information to the abstract without exceeding the word limit. However, we believe the addition of above examples related to COI types helps to clarify what are the COI related concerns. We have also added additional material to the Background to clarify., specifically, “Substantial evidence indicates that industry funding of biomedical research and author financial conflicts of interest (COI) arising from financial relationships with medically-related industry can bias research results” p. 3)

Background:

- Perhaps note the comparison group: “Available evidence indicates that industry-funded trials can be up to 5.4 times more likely to return positive results.[8] and trials with author COI may be as much as 8.4 times more likely to return favorable results.[6]” (Comparator groups are now identified- thank you for the suggestion. p. 3)

- Specify nature of effects, i.e “measurable [adverse] effects on biomedical research” (We now clarify that COI have been shown to associate with “reduced drug and device safety”, “adverse effects on the methodological quality of clinical trials”, “premature trial termination”, and “non-reporting of trial results”. p. 3)

- It would be helpful to define what “efficacy” means in the context of a COI policy – how would this be indicated/measured? (Although the original use of the term “efficacy” was deleted in revision, we have clarified this point further. The Background section has been substantially rewritten to indicate that “efficacy” refers to policy distinctions that are grounded in evidence about the differential risks of different COI types. Specifically, we added “If one were to assess the efficacy of COI policies (i.e., determine if COI policies have any effects on the quality of research), one must first assess whether policies stratified by COI types are grounded in evidence about the differential risks of different COI types.” p. 6)

- What is meant by “Competing guidelines for stratified COI policy”? The language is a bit confusing given the common use of ‘competing interests’ as a name for these kinds of policies. (The term “competing” has been removed and our revision clarifies that different guidelines appear to assume different risk profiles for different COI types and subsequently have different levels of restriction based on those assumptions of risk.)

- Pg 2. Is there a more elegant way to state “the holder of the relationship”? (We have changed this to “the recipient of remuneration.” p. 4)

- It would be interesting to see an example of: “They do not always agree on the severity of different COI.” (pg. 2) The US DHHS example is not particularly illustrative as it is a threshold for disclosure not

an acceptable/prohibited COI. (The first full paragraph on pg. 4 compares differential policy recommendations for consulting fees and industry representative access to AMCs, and Table 1 provides a fuller picture of policy differences. The US DHHS example has been relocated to a later paragraph on page 4 and we now better clarify that COI financial amount is used to set disclosure thresholds more often than establish COI prohibitions, p. 4.)

- I did not understand this sentence: “The substantial investments in establishing differential policies involve stratifying the risk to the research enterprise based on COI type and magnitude.” What are the substantial investments referring to? (This sentence has been removed and replaced with the new paragraph on the top of page 6. This paragraph clarifies that the establishment of stratified policies and stratified policy assessment regimens suggests that various stakeholders are making assumptions about differential risks associated with various COI types.)

Methods

- The tense seems to shift a bit and the sections written in active voice/first person were much more readable. (We have revised to include more active voice and first person where possible.)

Results

- line 3, pg 8, do you mean that 35 studies considered industry sponsorship of the study and author COI with a company to be the same phenomenon? You then state that “isolated assessments of author COI did not show up until 2005”. These points seem to belong together and perhaps require a bit more explanation in the text as this may be a key methodological finding/consideration. (The last paragraph of the introduction now forecasts the issue of variable disaggregation and the new material on the bottom of page 10 now better clarifies that the 35 studies used author employment in industry or other author COI as part of the inclusion criteria for a variable identified as “industry funding” or “industry sponsorship.”

- line 40, pg 10, what is meant by ‘funding disclosure practices’ in: “Relationships between COI or funding disclosure practices and outcomes of interest.” Does this refer to ‘actual’ versus ‘reported’ COI? I find this a difficult distinction because apart from Open Payments or other industry sources of data on financial relationships, nearly all COI data is ‘reported’. (yes- this is correct, and has been clarified more specifically in the new COI Variable Assessment section on page 12: “Most studies that evaluated author COI relied on the data in the published disclosure statement. A handful of studies used the authors institutional affiliation as an indicator of industry employment, and a few studies also compared disclosure statements to data available in the Open Payments Database.”)

- I think Table 2 could be more impactful if it was organized by DV Type rather than study. Then, readers could compare the body of findings more easily. (All studies except for one assessed the same DV and the outliner happens to be the last study in alphabetical order. Reordering the rows by DV type would not change the order of data presentation.)

Discussion/Conclusion

- Given that the Cochrane review provided rigorous and unambiguous evidence about the relationship between industry sponsorship and research outcomes, I was surprised that an additional 92 articles were identified that were published since 2016. I wonder if the authors might comment on this? (We have now commented on this specifically in the conclusion where we state: “Unspecified calls for “more research” might partially explain why, despite the clear findings of the 2017 meta-study [2], so many studies continue to assess if COI has an effect rather than which COI have what effects and why.” p. 18)

- “The common treatment of COI as an undifferentiated category of industry funding compromises the ability to meaningfully discriminate between the potential effects of industry funding or author COI.”

Yes! I think this is such an important point. If the authors reframe this as a methodological review, I think these key points can be made more of and are the real contribution of this review. (Thank you for the encouragement. We agree and have done so per your suggestion.)

- The authors make important policy recommendations, but I might suggest that these be moved and further developed in the Discussion rather than in the Conclusion. (Thank you for this suggestion. We have moved the policy recommendations to the Discussion accordingly.)

- I may have missed it, but I did not feel this statement was supported by the Results: “the results of this scoping review further support recent recommendations for attention to institutional COI at AMCs.” (Since the strongest evidence for specific COI types related to industry employment, this suggests that AMCs may need to be more careful about the kind of collaboration with industry author that follows from institutional COI. We now explain this issue in more detail at the end of page 16: “Furthermore, the strongest evidence relates to author employment in industry, although specific instructions about disclosing employment have been removed from the latest ICMJE disclosure guidance. Given that collaborations with industry are a common form of institutional COI, and one not addressed by individualized COI policies, these findings support recent calls for greater attention to institutional COI at institutions that conduct biomedical research.”)

- The authors suggest that COI policies at AMCs may be predominantly informed by risks to clinical practice and medical education rather than biomedical research. While I agree, I think this is in part due to the core functions of AMCs and the fact that other institutions have COI policies related biomedical research that also cover these clinician scientists (e.g. funders, journals etc). I think this point needs to be addressed in both the Introduction and the Discussion and the focus on AMC policies either expanded or justified. (We have broadened our focus throughout the manuscript to better clarify that our results apply to a broad range of institutions where biomedical research is conducted.)

VERSION 2 – REVIEW

REVIEWER	Joel Lexchin York University, School of Health Policy & Management
REVIEW RETURNED	15-Jul-2022

GENERAL COMMENTS	The revisions that the authors made have dealt with my initial concerns but there is one point that still remains. The authors state that the Cochrane review by Lundh et al., (their reference 2) looked at both industry sponsorship and author COI but that is not correct. Lundh only examined the effects of industry sponsorship.
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REVIEWER	Quinn Grundy University of Toronto, Lawrence S Bloomberg Faculty of Nursing
REVIEW RETURNED	22-Jul-2022

GENERAL COMMENTS	Thank you for the opportunity to re-review this important manuscript. The authors have well-addressed my previous (and lengthy - my apologies!) comments and I found the manuscript to be greatly strengthened. In particular, the reporting is very clear, and the rationale for the study and the conclusions it draws are compelling, timely, and action-oriented. I offer a few very minor comments in reviewing the revised manuscript: Abstract (Methods): I did not understand what was meant by “if they
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	<p>were operationalized as dichotomous” from the abstract alone. Could you clarify or provide an example?</p> <p>What is meant by “guidelines” in the abstract conclusion, “though most policies stratify guidelines [for managing COI?]”</p> <p>You might consider specifying at the end of the abstract conclusion to, “effectively inform policy to. . . [prevent COI? Manage COI? Mitigate bias?]”</p> <p>In the first sentence of the second paragraph of the intro, I might suggest continuing to make the distinction between industry sponsorship and COI as these tend to be addressed by very different policies within universities (e.g. contracts and grants for industry funded agreements, faculty-targeted COI policies). The following paragraphs address researcher COI, but do not really touch on industry research grants (paid to the institution), which is what is covered by the literature cited in the first paragraph (e.g. associated between industry sponsorship and outcomes). You make some really important comments about this in the Discussion and may want to foreshadow this up front.</p> <p>I think a word may be missing in this sentence (pg. 6 line 42), “the establishment of approaches to COI management that differentiate by type magnitude COI indicate that . . .”</p> <p>The justification for the study design could be stated more succinctly for clarity (p. 9 line 48), “identifying the extent to which assessments the effects of industry funding and COI on biomedical research were conducted in such a way that could support current COI policy stratifications.”</p> <p>You might consider a brief comment in the Discussion about the limitations faced by the included studies – I imagine that the reason that many studies did not perform stratified analyses, for example, might be that the information available (such as in disclosure statements) was so poorly reported so as to preclude such analyses.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Joel Lexchin, York University

Comments to the Author:

The revisions that the authors made have dealt with my initial concerns but there is one point that still remains. The authors state that the Cochrane review by Lundh et al., (their reference 2) looked at both industry sponsorship and author COI but that is not correct. Lundh only examined the effects of industry sponsorship.

RESPONSE: Thank you for this note and your continued review of our work. We have now corrected our description of how the Lundh paper addresses author COI the methods section on page 7. Specifically, we have removed “and author COI” from two sentences describing the paper, and added the following clarifying sentence: “While the meta-analysis did not expressly evaluate author COI as an isolated variable, “conflicts of interest” was a key term in the search strategy, and many articles included in the Cochrane review used COI as proxy for industry funding.”

Reviewer: 2

Dr. Quinn Grundy, University of Toronto

Comments to the Author:

Thank you for the opportunity to re-review this important manuscript. The authors have well-addressed my previous (and lengthy - my apologies!) comments and I found the manuscript to be greatly strengthened. In particular, the reporting is very clear, and the rationale for the study and the conclusions it draws are compelling, timely, and action-oriented.

RESPONSE: Thank you for your encouragement and continued engagement with our work.

I offer a few very minor comments in reviewing the revised manuscript:

Abstract (Methods): I did not understand what was meant by “if they were operationalized as dichotomous” from the abstract alone. Could you clarify or provide an example?

RESPONSE: There is insufficient room left in the abstract word budget for extensive clarification, but we rephrased “operationalized as dichotomous” to “assessed dichotomous variables” to further clarify and added a brief aside as an example: “(i.e., conflict present or absent).”

What is meant by “guidelines” in the abstract conclusion, “though most policies stratify guidelines [for managing COI?]”

RESPONSE: We have added “for managing COI” to the passage in question to clarify.

You might consider specifying at the end of the abstract conclusion to, “effectively inform policy to . . . [prevent COI? Manage COI? Mitigate bias?]”

RESPONSE: Thank you for this suggestion. We have changed this to “effectively inform policy to manage COI” per this suggestion.

In the first sentence of the second paragraph of the intro, I might suggest continuing to make the distinction between industry sponsorship and COI as these tend to be addressed by very different policies within universities (e.g. contracts and grants for industry funded agreements, faculty-targeted

COI policies). The following paragraphs address researcher COI, but do not really touch on industry research grants (paid to the institution), which is what is covered by the literature cited in the first paragraph (e.g. associated between industry sponsorship and outcomes). You make some really important comments about this in the Discussion and may want to foreshadow this up front.

RESPONSE: We have added “and industry funding” where indicated to preserve the distinction. We have also added an additional sentence foreshadowing the relevant comments in the discussion: “These include both policies designed to manage the risks associated with individual researcher COIs and guidelines addressing potential institutional COI resulting from industry gifts and research sponsorship.” Thank you for this idea for highlighting a key idea in the discussion.

I think a word may be missing in this sentence (pg. 6 line 42), “the establishment of approaches to COI management that differentiate by type magnitude COI indicate that . . .”

RESPONSE: We have corrected this sentence.

The justification for the study design could be stated more succinctly for clarity (p. 9 line 48), “identifying the extent to which assessments the effects of industry funding and COI on biomedical research were conducted in such a way that could support current COI policy stratifications.”

RESPONSE: We have edited the sentence as recommended. It now reads: “A methodological review is the ideal approach for this study, which requires identifying if research on the effects of industry funding and COI has been conducted in ways that could support current COI policy stratifications.”

You might consider a brief comment in the Discussion about the limitations faced by the included studies – I imagine that the reason that many studies did not perform stratified analyses, for example, might be that the information available (such as in disclosure statements) was so poorly reported so as to preclude such analyses.

RESPONSE: We concur completely. Thank you for this recommendation. We have added two additional notes to the discussion on pages 15 and 16. The first recognizes that variable disclosure statements limit what can be accomplished in terms of stratified COI research designs (“These findings point to limitations in current disclosure practices that allow authors a great deal of latitude in reporting and describing COI. The variability of disclosure statements limits the extent to which research on COI can evaluate differential effects.”) And, the second incorporates this point into our recommendations for the development of robust COI taxonomies (“Empirically validated taxonomies could also support more consistent disclosure practices, which would aid future research evaluating the differential effects of COIs by type or magnitude.”)