

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Sunshine on KOLs: Assessment of the nature, extent and evolution of financial ties between the leaders of professional medical associations and the pharmaceutical industry in France from 2014 to 2019: a retrospective study.
<b>AUTHORS</b>	CLINCKEMAILLIE, Marie; SCANFF, Alexandre; Naudet, Florian; BARBAROUX, Adriaan

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Ray Moynihan Bond University , Centre for Research in Evidence-Based Practice
<b>REVIEW RETURNED</b>	27-Apr-2021

<b>GENERAL COMMENTS</b>	<p>General comment</p> <p>Thank you for the opportunity to review this important study. I am making the same comments to authors and editors. As a general comment, consider using KOLs instead of KOL when talking about more than one person. Consider replacing the words “links of interest” with “financial ties” or “financial conflicts of interest” which are more commonly used phrases. Consider a final polish of the English. Generally the English is very good, but occasionally it could be improved just a little. I give a small example below. An important caveat is that I have no bio-stat expertise. One question: It is not clear to me whether you included all ties of a KOL, even if for example you included gifts from 2014 to a person who was a board member in 2020. It might be good in the Methods to mention explicitly what you did in relation to these historical ties. Forgive me if I missed it.</p> <p>Title Consider a revised title, which explicitly mentions the leaders of professional medical associations – as these were the people you examined. I understand they can also be called KOLs, but for me the word KOL is broader. You could still keep KOL and mention leaders of professional medical associations. P3, L 17. I am unsure what you mean by “agreements” – perhaps make clearer. Do you mean “contractual agreements” ? Perhaps you could explain in the Introduction with a few words what “agreement” covers. (I read later the definitions on p5 L 31 and in Table 1- ....so perhaps some brief mention of this earlier in Abstract and Introduction would help the reader. Despite all my work in this area, I was unsure what was meant.) P3, L23. I think the second sentence of the Results section needs to be a bit clearer. It took me some time to work out that the 12.3 M Euros was the total amount of the KOL. (similar comment for lines</p>
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	<p>27/28) Line 30/31 is a good example of being clearer.</p> <p>P3, L 46-47. Consider “cross checked” instead of “crossed”</p> <p>P3, L54, consider “raise the question” rather than “ask the question” as (I think) this is better English. So the sentence could be: “The major links between key opinion leaders and industry raise the question of the independence of these experts, as well as concerns that guidelines may be influenced by industry.”</p> <p>P4, L 5-6. Here is another small example of the need to slightly improve the English – I suggest a “the” before pharmaceutical. I will not continue to suggest small revisions like this – as I am sure the authors can arrange for a final polish of the English.</p> <p>P4 L6-7. Consider adding a reference to this first sentence of Introduction – and you could easily use your current reference #33. (Moynihan et al BMJ)</p> <p>P4, L13-14. I understand you may be limited with your number of references – and I imagine you may already be familiar with this reference – but if not – you may find this valuable as it is very central to the point you make in this final sentence of the first paragraph. I am not suggesting you need to reference it – just adding it here for your information. “Moynihan RN, Cooke GP, Doust JA, Bero L, Hill S, Glasziou PP. Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. PLoS Med. 2013 Aug;10(8):e1001500”</p> <p>P4, L28, “broad” should be “board”</p> <p>P4, L36-38 This sentence could be clearer and perhaps you mean “received” not “perceived”?</p> <p>P4, L56-58 It is not entirely clear to me what you mean by mentioning Google Scholar and the academic medical library . Also, it would be valuable to have a little more detail on the searching – even perhaps with an example of a search string if you have one.</p> <p>P5 L5. Consider adding this information into Abstract (ie board members between 2018 to 2020)</p> <p>P7 First paragraph...consider adding the finding of gift variation into the Abstract – it is very important (and echoes our US finding in BMJ 2020 ) And perhaps mention whether or not there was variation for the other two elements (remunerations and agreements)</p> <p>P7 – A limitation of my review is that I do not have bio-statistics expertise. However, I wonder whether it is possible to see if the differences between KOL and non-KOL (eg p7 L18-20) are “significant” statistically. Ifs that’s possible – it may be worth considering.</p> <p>P8, L11. You need to specify the period, not just say “this” period.</p> <p>P8 I think your finding of 83% of KOL having financial ties to industry is very powerful – I think you need to make more of it in Discussion – perhaps leading with it.</p> <p>P9, L4-5 I suggested using “leaders” or “board members” rather than “executives” (because for example Chief Executive Officers were not included, unless that were a member of the board or governing council)</p>
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<b>REVIEWER</b>	Lisa Parker The University of Sydney, Centre for Values, Ethics and the Law in Medicine
<b>REVIEW RETURNED</b>	14-May-2021

<b>GENERAL COMMENTS</b>	BMJ Open review “Sunshine on KOL” in France Synopsis This paper describes a cross-sectional study of pharmaceutical and device industry payments to KOL in France. The authors used a
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	<p>public database of industry payments, and cross-checked payments against a list of Board and council members in all the medical professional associations that recently produced guidelines. They found that KOL were over-represented with regard to monetary value of industry gifts, agreements and remuneration compared to general French physicians.</p> <p>Review – overall</p> <p>This paper is a useful addition to the growing literature describing and analysing the financial links between pharmaceutical and device industries with medical doctors. There are some issues that I recommend the authors clarify.</p> <p>Scope</p> <p>According to the authors, the French database of payments to doctors covers both the pharmaceutical and device industries. However throughout the paper (including the title) the authors refer only to the pharmaceutical industry. This needs clarification.</p> <p>Methods</p> <p>The definition of ‘agreements’ seems to be a bit back-to-front, whereby the authors provide a definition for conventions instead of agreements. Drawing on Table 1, I suggest rewording that sentence to read something like: ‘agreements are contracts or conventions involving ...’ Since this topic becomes an important focus in the Discussion, I also suggest the authors consider including some examples of what kinds of agreements might be listed here. For example, what might a physician expect in return for entering into an agreement to speak for a pharmaceutical industry at a congress? Table 1 suggests transport and accommodation but it’s not clear to me why that wouldn’t be categorised as a Gift and therefore listed in the gift database. The other examples in Table 1 of agreements are also not clear to me. Some more clarity around this would help the reader understand whether or not it was plausible for so many of these agreement amounts to be recorded as null. It’s possible that there is no formal guidance on this, but perhaps the authors have experiential knowledge from their own practice or that of colleagues about what goes on here.</p> <p>Results</p> <p>P8 The authors discuss ideas about why the amounts of money in this study are different to US studies. They suggest the US has enforcement measures and effective penalties – which begs the question, what are the enforcement measures and penalties in France ?</p> <p>P8 The authors suggest further research including department heads at teaching hospitals and medical university lecturers. Can they provide any references about investigation of industry payments to these groups of people in other countries?</p> <p>There are several minor typographical errors throughout</p> <p>p2line 49 ‘included’</p> <p>p3 line 6 ‘industry’</p> <p>p3 line 28 ‘board’</p> <p>Overall though, this is an important, and well conducted study and I look forward to seeing it published.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Mr. Ray Moynihan, Bond University

Thank you for the opportunity to review this important study. I am making the same comments to authors and editors. As a general comment, consider using KOLs instead of KOL when talking about more than one person. Consider replacing the words “links of interest” with “financial ties” or “financial conflicts of interest” which are more commonly used phrases. Consider a final polish of the English. Generally the English is very good, but occasionally it could be improved just a little. I give a small example below. An important caveat is that I have no bio-stat expertise. One question: It is not clear to me whether you included all ties of a KOL, even if for example you included gifts from 2014 to a person who was a board member in 2020. It might be good in the Methods to mention explicitly what you did in relation to these historical ties. Forgive me if I missed it.

Thank you for the time you spent reviewing this study and your constructive comments.

We have corrected KOLs when needed and replaced the words “links of interest” with “financial ties” as suggested.

A native English Speaker completed a final review just before resubmission.

We included all the ties of a KOL starting from 2014, if the KOL was a board member in 2018, 2019 or 2020. We clarified this in the first paragraph of the Methods section with the sentence “As per our protocol (registration number: osf.io/m8syh), we took into consideration the financial ties of each KOL from 2014 to 2019. KOLs were defined as board members of an association from 2018 to 2020.”

Title

Consider a revised title, which explicitly mentions the leaders of professional medical associations – as these were the people you examined. I understand they can also be called KOLs, but for me the word KOL is broader. You could still keep KOL and mention leaders of professional medical associations.

Done : “Sunshine on KOLs: Assessment of the nature, extent and evolution of financial ties between the leaders of professional medical associations and the pharmaceutical industry in France from 2014 to 2019: a retrospective study.”

P3, L 17. I am unsure what you mean by “agreements” – perhaps make clearer. Do you mean “contractual agreements” ? Perhaps you could explain in the Introduction with a few words what “agreement” covers. (I read later the definitions on p5 L 31 and in Table 1- ....so perhaps some brief mention of this earlier in Abstract and Introduction would help the reader. Despite all my work in this area, I was unsure what was meant.)

Thank you for the opportunity to clarify this point that was also raised by Lisa Parker. By agreements, we effectively meant contracts. As suggested, we replaced agreements by « contractual agreements » in most cases.

We also moved the definition of gifts, agreements and remunerations from the section **Identifying and extracting payment details** to the introduction.

The definition of agreements was clarified : ““Contractual agreements” involve obligations on both sides: participation in a congress, research or clinical trial activity, training action, etc.”

We added examples of agreements in table 1.

P3, L23. I think the second sentence of the Results section needs to be a bit clearer. It took me some time to work out that the 12.3 M Euros was the total amount of the KOL. (similar comment for lines 27/28) Line 30/31 is a good example of being clearer.

Thank you. We rephrased the sentences in a shorter way.

P3, L 46-47. Consider "cross checked" instead of "crossed"

Done.

P3, L54, consider "raise the question" rather than "ask the question" as (I think) this is better English. So the sentence could be: "The major links between key opinion leaders and industry raise the question of the independence of these experts, as well as concerns that guidelines may be influenced by industry."

Thank you for your comment. Unfortunately, we had to remove this sentence because the editor asked us to keep only sentences that specifically relate to the methods.

P4, L 5-6. Here is another small example of the need to slightly improve the English – I suggest a "the" before pharmaceutical. I will not continue to suggest small revisions like this – as I am sure the authors can arrange for a final polish of the English.

Done. Thank you.

P4 L6-7. Consider adding a reference to this first sentence of Introduction – and you could easily use your current reference #33. (Moynihan et al BMJ)

Done.

P4, L13-14. I understand you may be limited with your number of references – and I imagine you may already be familiar with this reference – but if not – you may find this valuable as it is very central to the point you make in this final sentence of the first paragraph. I am not suggesting you need to reference it – just adding it here for your information. "Moynihan RN, Cooke GP, Doust JA, Bero L, Hill S, Glasziou PP. Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. PLoS Med. 2013 Aug;10(8):e1001500"

Done. Great paper!

P4, L28, "broad" should be "board"

Thank you for pointing this out.

P4, L36-38 This sentence could be clearer and perhaps you mean "received" not "perceived"?

Thank you. We clarified the sentence as follows: "This paper uses the data from the Transparency in Healthcare database to describe the nature, the extent and the evolution of the financial ties of all physicians in France, with a focus on key opinion leaders (KOLs). The ties of professional medical associations were assessed by grouping the gifts, contractual agreements and remunerations received by the KOLs of each professional medical association."

P4, L56-58 It is not entirely clear to me what you mean by mentioning Google Scholar and the academic medical library. Also, it would be valuable to have a little more detail on the searching – even perhaps with an example of a search string if you have one.

We apologize for the lack of precision in the way the searching was described. We rewrote the **Identifying professional medical associations** section as follows : “The BML website is an academic medical library that lists month by month all the consensus statements, guidelines and recommendations published in French. MC conducted a search through it from January 2018 to December 2019 and selected all the national professional medical associations regardless of the nature of the publication they were listed for. The next step was to examine the Cismef website, which has a “learned society” section that lists French speaking professional medical associations. MC selected all the professional medical associations in France from that list. Finally, MC used the “Le Parisien” database that lists French learned societies, and selected all the professional medical associations in the “medical science” section. Duplicates were then eliminated and MC examined the associations one by one to determine whether they had published guidelines in 2018 or 2019. To do so, BMLweb was used first and then the search engine for clinical practice guidelines of the Cismef website if there was no match on BMLweb, and finally Google Scholar and the association website.”

P5 L5. Consider adding this information into Abstract (ie board members between 2018 to 2020)

Done.

P7 First paragraph...consider adding the finding of gift variation into the Abstract – it is very important (and echoes our US finding in BMJ 2020) And perhaps mention whether or not there was variation for the other two elements (remunerations and agreements)

Added in the abstract. This variation was also found for the other two elements since the two terminals of the IQR (Inter Quartile Range) are separated by a factor of 70, similarly for the three elements. That means that the top quartiles' ties are at least 70 times higher than the first quartile.

In order to clarify, we added “and also varied widely” before the IQR in the results and in the discussion: “The number and value of gifts, agreements and remunerations for all the members of a single association varied widely from one association to another.”

P7 – A limitation of my review is that I do not have bio-statistics expertise. However, I wonder whether it is possible to see if the differences between KOL and non-KOL (eg p7 L18-20) are “significant” statistically. Ifs that’s possible – it may be worth considering.

Statistical tests are not really adapted to big databases because with such a large number of observations,  $p$  is almost systematically  $< .05$ , even when the difference is slight. Simply put, statistical analyses are used to determine whether the difference between two samples is related to a sampling error or reflects a real difference between the two populations. Here, we have included the whole population, so the sampling error is neglectable when compared with the bias described in the “limitations” section. We preferred to seek an interpretation of the difference using percentages rather than putting forward statistical tests.

P8, L11. You need to specify the period, not just say “this” period.

Done.

P8 I think your finding of 83% of KOL having financial ties to industry is very powerful – I think you need to make more of it in Discussion – perhaps leading with it.

Thank you. We added the sentence “83% of the KOLs received at least one gift from the pharmaceutical industry from 2014 to 2019, for a total amount of €12.3M.” in the first paragraph of the discussion.

P9, L4-5 I suggested using “leaders” or “board members” rather than “executives” (because for example Chief Executive Officers were not included, unless that were a member of the board or governing council)

Thank you. Done.

Reviewer #2 : Dr. Lisa Parker, The University of Sydney

Review – overall

This paper is a useful addition to the growing literature describing and analysing the financial links between pharmaceutical and device industries with medical doctors. There are some issues that I recommend the authors clarify.

Scope

According to the authors, the French database of payments to doctors covers both the pharmaceutical and device industries. However throughout the paper (including the title) the authors refer only to the pharmaceutical industry. This needs clarification.

Thank you for your comment and the opportunity to clarify that point. We gathered the pharmaceutical and device industries under the single term of “pharmaceutical industry” in our work for more convenience and because the database deals with them the same way.

We added “For more convenience, this paper will gather both pharmaceutical and medical device industries under the term “pharmaceutical industry.” at the end of the second paragraph of the introduction.

Methods

The definition of ‘agreements’ seems to be a bit back-to-front, whereby the authors provide a definition for conventions instead of agreements. Drawing on Table 1, I suggest rewording that sentence to read something like: ‘agreements are contracts or conventions involving ...’ Since this topic becomes an important focus in the Discussion, I also suggest the authors consider including some examples of what kinds of agreements might be listed here. For example, what might a physician expect in return for entering into an agreement to speak for a pharmaceutical industry at a congress? Table 1 suggests transport and accommodation but it’s not clear to me why that wouldn’t be categorised as a Gift and therefore listed in the gift database. The other examples in Table 1 of agreements are also not clear to me. Some more clarity around this would help the reader understand whether or not it was plausible for so many of these agreement amounts to be recorded as null. It’s possible that there is no formal guidance on this, but perhaps the authors have experiential knowledge from their own practice or that of colleagues about what goes on here.

Thank you for your comment on this point that was also raised by Ray Moynihan. We apologize for being unclear. As suggested, we replaced agreements by “contractual agreements” in most cases. We rewrote the agreements definition in the introduction :”Contractual agreements” involve obligations on both sides: participation in a congress, research or clinical trial activity, training action, etc.”

The word “convention” was mistakenly used for “agreements” in Methods, and we thank you for noticing it.

More examples of what an agreement could be were added in table 1 = Contracts involving obligations on the part of the physician and the industry. For example, participation in a congress as a speaker by the physician with payment for the lecture by the company, or participation at the presentation of a new medical device by the physician with payment for transport and accommodation by the company. The agreements concern research activities, clinical trials, participation in a scientific congress or training activities.

Therefore, a payment for transport or accommodation can be found either in the gift category or in the agreement category, depending on whether the physician provides a service in exchange for it or not (speech at a congress, participation at a presentation of a new device or medicine by the company).

**Results**

P8 The authors discuss ideas about why the amounts of money in this study are different to US studies. They suggest the US has enforcement measures and effective penalties – which begs the question, what are the enforcement measures and penalties in France ?

Thank you for your question. There are no enforcement measures nor effective penalties in France at this time so we modified the sentence as follows: “Finally, in the USA, there are more mandatory payments to report, and there are enforcement measures and effective penalties that do not exist in France”.

For your information, in France, a Sales Visit Charter promotes good practices such as the presentation of approved product information including side effects and contraindications. Despite strict regulations (health authorities can impose fines of up to €10,000 or 10% of a product’s annual sales revenues), the Sales Visit Charter is rarely respected. Free drug samples and gifts of food and drink in the office are not allowed in France, but GPs still receive gifts and invitations to restaurants since the law allows for exceptions (ref: Mintzes B, Lexchin J, Sutherland JM, Beaulieu M-D, Wilkes MS, Durrieu G, et al. Pharmaceutical sales representatives and patient safety: a comparative prospective study of information quality in Canada, France and the United States. J Gen Intern Med 2013;28:1368–75. <https://doi.org/10.1007/s11606-013-2411-7>).

Prescrire International. “15 Years of Monitoring and One Simple Conclusion: Don’t Expect Sales Representatives to Help Improve Healthcare Quality,”. La Revue Prescrire 15, no. 84 (2006): 154-159.”)

P8 The authors suggest further research including department heads at teaching hospitals and medical university lecturers. Can they provide any references about investigation of industry payments to these groups of people in other countries?

We talked about department heads at teaching hospitals and medical university lecturers as other possible influential physicians who could be included in a KOL definition and who would be interesting subjects to analyze. This would be particularly interesting because we have no reference of such investigations in other countries.

There are several minor typographical errors throughout  
p2line 49 ‘included’  
p3 line 6 ‘industry’  
p3 line 28 ‘board’

Corrections have been done. Thank you

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Ray Moynihan Bond University , Centre for Research in Evidence-Based Practice
<b>REVIEW RETURNED</b>	13-Sep-2021
<b>GENERAL COMMENTS</b>	Thanks for opportunity to re-review.  I feel the authors have addressed my comments from the initial review. I repeat the caveat that I have no bio-stats expertise, which explains my answer to question #7 above. I also have not checked



	<p>all of the many numbers and figures in the paper, but trust the authors have triple checked all their numbers.</p> <p>I only have one tiny comment about page 2:</p> <p>Page 2: “ To investigate the financial relationships between key opinion leader (KOL) or non-KOL physicians and pharmaceutical and device companies in France” This sentence is not entirely clear and sounds a little odd at present. Does it have to have “non-KOL” in it as well? Is this more accurate: “ To investigate the financial relationships between key opinion leaders (KOLs) and pharmaceutical and device companies in France, compared to non-KOL physicians”</p>
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<b>REVIEWER</b>	Lisa Parker The University of Sydney, Centre for Values, Ethics and the Law in Medicine
<b>REVIEW RETURNED</b>	17-Sep-2021

<b>GENERAL COMMENTS</b>	The authors have addressed all my concerns.
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