PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Disclosure of payments by pharmaceutical companies to healthcare professionals in the United Kingdom: analysis of the Association of the British Pharmaceutical Industry's Disclosure UK database, 2015 and 2016 cohorts
AUTHORS	Mulinari, Shai; Ozieranski, Piotr

VERSION 1 – REVIEW

REVIEWER	Brian G. Choi Associate Professor of Medicine The George Washington University, USA
REVIEW RETURNED	18-Apr-2018

GENERAL COMMENTS	The authors have undertaken a challenging analysis of a messy database and revealed many of its flaws. Because of the variable reporting standards by companies, analysis and interpretation are difficult and bring to question whether there is something actually nefarious or merely reflect the messiness of these data. The authors imply that there are data being withheld from disclosure. What are the consequences to non-disclosure? Can these companies be penalized? If not, perhaps that explains why there is such messy disclosure. If they can be penalized, this analysis takes substantially greater importance – please expand on these consequences. Is reporting by pharmaceutical companies voluntary? If it's voluntary, any insight into differences between companies that do not disclose vs those that do? Adding to the messiness, the disclosure categories lend themselves to considerable ambiguity. If a TOV was so that a principal investigator could travel to and present at a scientific meeting, could that avoid disclosure since that is for "Research" or may have it been disclosed as an Event? Similarly, if one entertained with a fancy meal at a restaurant at a meeting, was that disclosed as part of "accommodations" or not disclosed since that was for food? Exploration of the disclosure rules is also necessary to determine whether the discrepancies could be from different interpretation of vague guidelines. The authors conclude that large payments are concealed because the percentage number of TOVs exceeds the percentage of monies disclosed. However, what if the consultancy payments were for 0 pounds (as may be the case with stock options that then become valueless if underwater)? Or what if the payment was not to the individual but to the HCPs' organization? Could that explain this difference? Concluding that the payments are being concealed is

	possible but alternative explanations should at least be entertained. The comparison to the US Open Payments database is tangential and takes away from the description of the Disclosure UK database. The way in which the authors present data from the Disclosure UK database could benefit from being simplified and might be more worthy of inclusion in the manuscript than a comparison to the Open Payments database given how different they are—i.e. Open Payments includes individual level data, has far more categories with pre-specified inclusion criteria, is required of all pharmaceutical and group purchasing organizations, and provides a more granular level of detail, to name a few. Additionally, the statement that the Disclosure UK database includes more breadth is misleading as the Open Payments database includes optometrists, dentists, and chiropractors, as well. As a style point, please minimize editorializing and speculating on reasons for findings in the Results section – these comments are better placed in the Discussion. Page 5, line 26-29: What are the differences noted and are these discrepancies still noted going forward? Page 7, lines 39-40: The authors discuss that approximately 10 percent of companies were excluded from the analysis regarding company level payments—did the results change when including these companies versus not? A sensitivity analysis or comment regarding that a sensitivity analysis was done would enhance this. Page 13, Lines 29-40: Regarding the discussion of individual level payments, is it factually correct to say that the companies are concealing larger disclosures if the lack of individual level data is based on an individual HCPs decision whether or not to have their information included at the individual level? A truer, albeit difficult hypothesis to test, might be that HCPs who receive larger payments are more likely to choose not to be included at the individual level, though this is subject to the limitations previously described regarding the aggregate level data. Again, regarding individual vs. aggregate data discussed on Page 14, Lines 38-67, this might be subject to the same limitations as above given that individual level reporting lies on the HCP. On p 15, lines 10-11, the authors revealed that they defined any difference greater than one percentage point as being discordant – this belongs in the Methods section and should be explained there. Page 16, Lines 19-30: This would be a place to discuss why the authors believe these companies vary substantially. If individually reported data is contingent on HCP reporting, wouldn't one expect this to be consistent across companies? On p 17, line 19, the authors state that "companies should never leave cells empty." Was this permissible in Disclosure UK? If so, the companies were operating within bounds and this is the authors opinion as to how Disclosure UK should change.

REVIEWER	Tim Kinnaird University Hospital of Wales
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	Introduction too long and much of it is like a discussion Tables 1 and 2 could be supplementary Methods incredibly long and tortuous and extend into discussion. Need to be made shorter and clearer Overall there are a few interesting points here but they are lost in the style of the manuscript. If the authors such to publish in general medical journal they should be extensively revised to be shorter, punchier and clearer.

REVIEWER	Jacob Simmering Post-Doctoral Scholar Department of Computer Science University of Iowa United States
REVIEW RETURNED	13-Jun-2018

GENERAL COMMENTS	Mulinari and Ozieranski present an interesting analysis of disclosures made by pharma companies to healthcare professionals in the UK. Their analysis indicates a number of limitations of the database - especially the ability of HCPs to opt out of disclosure reporting. The summary figures presented suggest a relationship between consultancy-related payment size and the propensity to accept identification in the disclosure. I have a few minor notes: Page 8, line 22 - is the number of companies excluded for not reporting aggregate payments in 2016 n = 12 or n = 13 (the number mentioned on page 7, line 40)? Use of "," as decimal separator in page 8, line 32 and page 12, line 21 instead of the "." used elsewhere.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Brian G. Choi
Institution and Country: The George Washington University, USA
Please state any competing interests or state 'None declared': None declared. My student Ramzi Dudum and I researched the Open Payments database which is sufficiently unrelated to the current research. Dr. Dudum contributed to this review.

Please leave your comments for the authors below
• The authors have undertaken a challenging analysis of a messy database and revealed many of its flaws. Because of the variable reporting standards by companies, analysis and interpretation are difficult and bring to question whether there is something actually nefarious or merely reflect the messiness of these data. The authors imply that there are data being withheld from disclosure. What are the consequences to non-disclosure? Can these companies be penalized? If not, perhaps that explains why there is such messy disclosure. If they can be penalized, this analysis takes

substantially greater importance – please expand on these consequences.

Response: Thank you for this very important comment. As we note in various places in the text, non-disclosure refers to instances where HCPs have not accepted to have their name/details in the database. One key finding of our study is that the level of HCP non-disclosure differs substantially across companies. This fact suggests that company characteristics are an important factor in determining HCP consent, which could, for example, reflect differences in policies for collecting consent from HCPs. Thus non-disclosure does not automatically mean that a company is withholding information – some companies may simply do a better job at securing HCP consent than others, or they may be "unlucky" to have collaborated with doctors that are unwilling to disclose. Nevertheless, the fact that, for example, Merck Sharpe & Dohme was only able to secure consent for fewer than 2% of their payments in 2015 does suggest that at least some companies may have ignored their stated commitment to disclosure, and the reviewer is right to ask if such behaviour could be penalized.

The answer is yes: Companies can be sanctioned by the Prescription Medicines Code of Practice Authority (PMCPA), which is the industry self-regulatory body that operates the ABPI Code of Practice. Specifically, Clause 24 of the ABPI Code stipulates that, "Companies must document and publicly disclose certain transfers of value made directly or indirectly to health professionals and healthcare organizations located in Europe." That is, if a company omitted information or displays a lack of commitment to Disclosure UK, it should be sanctioned by the PMCPA. Investigation of complaints regarding such behaviour would follow the same procedure as with any other potential violation of the ABPI Code. We have detailed the workings of the UK self-regulatory system in previous publications (Zetterqvist et al 2015; Vilhelmsson et al 2016), and argued that the financial sanctions levied by the PMCPA on violating companies (only a couple of thousands of pounds) are highly unlikely to deter corporate misconduct. We do not want to repeat such arguments here but in the Discussion we have included the following comment regarding the need to investigate whether lack of disclosure reflects violations of the ABPI Code:

"Notably, companies that fail to live up to industry's stated commitment to Disclosure UK could be investigated and sanctioned by the Prescription Medicines Code of Practice Authority (PMCPA), the industry self-regulatory body that administers the ABPI Code of Practice.9 10 Although a lower than average HCP consent rate does not prove company misconduct the fact that, for example, Merck Sharpe & Dohme reported that fewer than 2% of collaborating HCPs consented to individual-level disclosure in 2015 suggests that the PMCPA has reason to investigate whether some companies have eschewed disclosure."

• Is reporting by pharmaceutical companies voluntary? If it's voluntary, any insight into differences between companies that do not disclose vs those that do?

Response: Reporting is voluntary in the legal sense that there is no law in the UK forcing companies to report payments. However, all companies that are members of the ABPI – and this includes all major "research-based" firms and most medium-size ones – have agreed to report payments. In this sense, reporting is not voluntary for ABPI members and, as noted in the previous response, companies that eschew disclosure should be sanctioned by the PMCPA. In addition, some firms, including some smaller, local UK-based firms, that are not ABPI members have voluntarily chosen to abide by the ABPI Code and participate in Disclosure UK. In the Appendix we provided a list of all companies that report payments in the database – in total over 100 firms. Collectively, these firms are responsible for most non-generic prescription drugs in the UK. We have added in the Introduction that:

"All ABPI members and any other pharmaceutical company that follows ABPI's Code of Practice for the Pharmaceutical Industry are required to report payments; in total, over one hundred companies."

• Adding to the messiness, the disclosure categories lend themselves to considerable ambiguity. If a TOV was so that a principal investigator could travel to and present at a scientific meeting, could that avoid disclosure since that is for “Research” or may have it been disclosed as an Event? Similarly, if one entertained with a fancy meal at a restaurant at a meeting, was that disclosed as part of “accommodations” or not disclosed since that was for food? Exploration of the disclosure rules is also necessary to determine whether the discrepancies could be from different interpretation of vague guidelines.

Response: We agree that there may be room for different interpretations of rules. As we note in the Limitations section, “Given the complexity, these methodological matters should become the subject of a separate study.” Such a study would involve conducting a detailed reading of companies “methodological notes”, and perhaps even interviews with company representatives and HCPs, which we believe is beyond the scope of this paper.

Regarding the specific examples provided by the reviewer, as we noted in Table 1 (now in Appendix) the rule governing “Events” state that only “costs that are clearly related to R&D” can be excluded, and paying for a PI’s trip is unlikely to qualify as “clearly” R&D.

Regarding costs for food, the ABPI Code states “The cost of a meal (including drinks) provided by way of subsistence must not exceed £75 per person, excluding VAT and gratuities.” and, as we read the Code, and as has been reported elsewhere (Fabbri et al 2018), such payments are not disclosed by companies. We write in Limitations section:

“Furthermore, transparency requirements do not apply to manufacturers of generics and over-the-counter medicines and exclude some payments such as food and drinks; thus, our analysis likely underestimates the true extent of payments”

• The authors conclude that large payments are concealed because the percentage number of TOVs exceeds the percentage of monies disclosed. However, what if the consultancy payments were for 0 pounds (as may be the case with stock options that then become valueless if underwater)? Or what if the payment was not to the individual but to the HCPs’ organization? Could that explain this difference? Concluding that the payments are being concealed is possible but alternative explanations should at least be entertained

Response: Thank you for this comment. First of all, we wish to clarify that the “concealment” referred to HCPs not companies. While we agree that one could come up with some alternative explanations, we believe that the most likely explanation is, as the reviewer notes below, that HCPs who receive larger payments for consultancies are more likely to choose not to be included at the individual level – and this is what we meant by “concealment of larger size payments for consultancies”. Notably, a more detailed analysis on a company-level (not in paper) shows that the difference in consultancy-related disclosure rates is seen for most companies. This observation suggest that HCP non-disclosure of larger-size consultancy payments is a general phenomenon and not specific to particular companies. For example, 19 of the 20 largest spenders in 2015 reported higher consent rates for consultancies in number than in monies (median 9% difference; range -11%-34%).

Companies making payments to the HCPs’ organisation is unlikely to explain such differences because those payments would either be reported in the healthcare organisation portion of the database (and therefore not contribute to our data) or in the HCP database (see Limitations section), but not in both. However, an alternative explanation, yet an unlikely one in light of the consistency we see across companies, is that a limited number of HCPs that have received extremely large consultancy-payments do not disclose but that, apart from those few individuals, there is no

relationship between payments size and tendency to disclose.

However, we do agree that our results do not prove concealment, and we have therefore removed this statement. Instead we state now neutrally that disclosure rates for consultancy-related payments were higher in number of TOVs than in monies. In the Discussion, we have added however that, “A likely explanation is that HCPs who receive larger consultancy payments are less likely to consent to disclosure.”

• The comparison to the US Open Payments database is tangential and takes away from the description of the Disclosure UK database. The way in which the authors present data from the Disclosure UK database could benefit from being simplified and might be more worthy of inclusion in the manuscript than a comparison to the Open Payments database given how different they are—i.e. Open Payments includes individual level data, has far more categories with pre-specified inclusion criteria, is required of all pharmaceutical and group purchasing organizations, and provides a more granular level of detail, to name a few. Additionally, the statement that the Disclosure UK database includes more breadth is misleading as the Open Payments database includes optometrists, dentists, and chiropractors, as well.

Response: We very much appreciate this comment. Although we believe the comparison to the US database is important from a policy perspective for exactly the reasons cited by the reviewer - i.e., it helps pinpointing deficiencies in Disclosure UK - we agree that it makes the text longer and messier than necessary and takes away from the description of the UK database. We have deleted the entire section and any reference to it elsewhere in the text. We believe that this deletion together with the additional changes we make in response to the Review and Editor comments has significantly helped streamline the text. However, we have added a sentence towards the end of the Discussion stating that:

"In the event that the ABPI is unable to swiftly resolve the various problems of limited transparency and data quality in Disclosure UK our study has revealed, we suggest – like others37 38 – that the UK government should consider introducing legislation requiring disclosure modelled on the US Open Payments Database."

We have also added in Abstract conclusion that: “If deficiencies remain unresolved, the UK should consider introducing legislation requiring obligatory disclosure to allow for adequate tracking of industry payments.”

• As a style point, please minimize editorializing and speculating on reasons for findings in the Results section – these comments are better placed in the Discussion.

Response: Thank you for this comment. We have removed speculations from Results section and moved them to the Discussion.

• Page 5, line 26-29: What are the differences noted and are these discrepancies still noted going forward?

Response: Thank you for this question. We explain this in the Methods:

“However, the ABPI has reported that although the majority of companies in the 2015 version of the database correctly understood the instructions on how to calculate this disclosure statistic, some companies appear to have misunderstood and instead provided the number of recipients disclosed in aggregate for each TOV type as per cent of all recipients that received payments from the company irrespective of TOV type”

Our results suggest that discrepancies were still there in 2016. In the Discussion we write “That the current consent rate reporting standard is unintuitive is underlined by the inconsistencies, and possible inaccuracies, in companies’ reporting, and which – despite being highlighted by the ABPI – continued into the 2016 version of the database.”

• Page 7, lines 39-40: The authors discuss that approximately 10 percent of companies were excluded from the analysis regarding company level payments—did the results change when including these companies versus not? A sensitivity analysis or comment regarding that a sensitivity analysis was done would enhance this.

Response: Thank you for this question. In the Appendix we provide the relevant company-level raw data. The excluded companies are the ones with the “N/A” label. These are predominantly minor companies and, collectively, they contributed to less than 2% of total spending. If we assume that these companies indeed reported 100% at the individual level, it would shift the company-level distribution in the following way (sensitivity analysis values in parenthesis):

In 2015, the median among companies for TOV sums was 47.3% (51.9%), with 75% of companies reporting more than 72.8% (81.3%) of sums and 25% of companies reporting less than 21.3% (26.2%) of sums at the individual level. By 2016 HCP consent rates had increased: median 57.7% (66,2%). Still, 25% of companies included in this analysis reported less than 38.6% (42.5%) of the value of payments at the individual level.

These are relatively small changes, and they do not affect overall conclusion that there is substantial variation in HCP disclosure rates across companies. We have added a comment about this in the Limitation section.

• Page 13, Lines 29-40: Regarding the discussion of individual level payments, is it factually correct to say that the companies are concealing larger disclosures if the lack of individual level data is based on an individual HCPs decision whether or not to have their information included at the individual level? A truer, albeit difficult hypothesis to test, might be that HCPs who receive larger payments are more likely to choose not to be included at the individual level, though this is subject to the limitations previously described regarding the aggregate level data.

Response: We are extremely thankful for this comment. As explained above It was not our intention to imply that companies were concealing larger payments but we can understand now how it might have been interpreted in this way. We very much agree that the most likely hypothesis is that HCPs who receive larger payments are more likely to choose not to be included at the individual level (see above). This was what we were referring to in this paragraph, and this is consistent with the corresponding methods and discussion sections. We have reworded to avoid risk of misunderstanding. To avoid risk of misunderstanding we now also talk about “consent” rather than “disclosure” throughout, e.g., we use the concept “HCP consent rate” rather than “disclosure rate. Thank you.

• Again, regarding individual vs. aggregate data discussed on Page 14, Lines 38-67, this might be subject to the same limitations as above given that individual level reporting lies on the HCP.

Response: We referred to companies disclosing payments because they are the ones reporting in the database not HCPs. However, to avoid the potential for misunderstanding we have reworded. Please see previous response.

• On p 15, lines 10-11, the authors revealed that they defined any difference greater than one

percentage point as being discordant – this belongs in the Methods section and should be explained there.

Response: Thank you. It has been deleted and is now only in Methods.

• Page 16, Lines 19-30: This would be a place to discuss why the authors believe these companies vary substantially. If individually reported data is contingent on HCP reporting, wouldn't one expect this to be consistent across companies?

Response: We can only speculate on possible reasons for difference but in the text we do suggest a possible explanation, namely "policies for collecting consent from HCPs, which in turn may be associated with more general corporate cultures, as another set of likely determinants of HCP disclosure consent."

We have been in contact with representatives from ABPI to ask for their input on this issue. They hypothesized, as we do, that it might be related to company polices. They also said to exclude some other possible explanation, such as company size and being UK-based/non-UK-based. We also believe that these company features are of limited explanatory value because we can see in the Appendix table that HCP consent rates vary substantially amongst high spenders and low spenders as well as UK-based and non-UK based companies, respectively.

• On p 17, line 19, the authors state that "companies should never leave cells empty." Was this permissible in Disclosure UK? If so, the companies were operating within bounds and this is the authors opinion as to how Disclosure UK should change.

Response: Yes, this our opinion and should be read as a recommendation. We have clarified this.

Reviewer: 2
Reviewer Name: Tim Kinnaird
Institution and Country: University Hospital of Wales, UK
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
• Introduction too long and much of it is like a discussion

Response: Thank you for this comment. We have substantially shortened the introduction.

• Tables 1 and 2 could be supplementary

Response: We have followed the reviewer's suggestion and made tables supplementary.

• Methods incredibly long and tortuous and extend into discussion. Need to be made shorter and clearer.

Response: We believe it is very important for the Methods to provide enough detail and explanation for others to be able to replicate our analysis using these and other datasets (i.e. future disclosures or for other countries). One should keep in mind that this, to the best of our knowledge, is the first detailed analysis of disclosure data in Europe. Also, we believe it is particularly important to be transparent about methods and definitions given the topic of the study, However, we have made a number of deletions in the Methods to streamline the text.

• Overall there are a few interesting points here but they are lost in the style of the manuscript. If the authors such to publish in general medical journal they should be extensively revised to be shorter, punchier and clearer.

Response: As noted in previous responses we have shortened parts of the text, and especially the introduction. We have also shortened and streamlined the Methods and Results sections and made other changes to the text to make it clearer. However, would like emphasize the need to provide substantial detail in order to provide insight into the database's structure and content and suggest ways to improve its transparency.

Reviewer: 3
Reviewer Name: Jacob Simmering
Institution and Country: Department of Computer Science, University of Iowa, United States
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Mulinari and Ozieranski present an interesting analysis of disclosures made by pharma companies to healthcare professionals in the UK. Their analysis indicates a number of limitations of the database - especially the ability of HCPs to opt out of disclosure reporting. The summary figures presented suggest a relationship between consultancy-related payment size and the propensity to accept identification in the disclosure.

• I have a few minor notes:

Page 8, line 22 - is the number of companies excluded for not reporting aggregate payments in 2016 n = 12 or n = 13 (the number mentioned on page 7, line 40)?

Response: Thank you. The correct number is 13.

• Use of "," as decimal separator in page 8, line 32 and page 12, line 21 instead of the "." used elsewhere.

Response: Thank you

VERSION 2 – REVIEW

REVIEWER	Dr Tim Kinnaird University Hospital of Wales
REVIEW RETURNED	18-Aug-2018

GENERAL COMMENTS	The authors have addressed my concerns

REVIEWER	Jacob Simmering University of Iowa
REVIEW RETURNED	18-Aug-2018

GENERAL COMMENTS	The revised and streamlined methods and results sections are much easier to read. The methods are clear and the results are presented in a straightforward manner. I see no cause for concern in the statistical inference or interpretation of the analyses.