PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does industry-sponsored education foster overdiagnosis and overtreatment of depression, osteoporosis and overactive bladder syndrome? An Australian cohort study
AUTHORS	Mintzes, Barbara; Swandari, Swestika; Fabbri, Alice; Grundy, Quinn; Moynihan, Ray; Bero, Lisa

VERSION 1 – REVIEW

REVIEWER	Bjørn Hofmann NTNU Gjøvik and University of Oslo, Norway
REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	This manuscript reports a retrospective cohort study that examined publicly reported industry-sponsored events in Australia from October 2011 to September 2015. The study investigated three conditions potentially subject to overdiagnosis, i.e., depression, osteoporosis, and overactive bladder. The outcome measures were event and attendee characteristics, sponsoring companies, related marketed treatments, cost-effectiveness ratings, and dispensing rates. The authors find that industry sponsorship of education on depression, osteoporosis, and overactive bladder focused on primary care and was concentrated among few companies that market medicines for each condition. As these products are subject to concerns about efficacy, safety, and cost-effectiveness, the authors raise questions about the focus of sponsored education. There are few studies of the associations between sponsored continuing medical education (CME) and specific conditions prone to overdiagnosis. The results are interesting, as they give knowledge previously not easily accessible. As such the study is original. The study also documents substantial CME activity for drugs with questionable cost-effectiveness, and thereby raises important moral questions. Nonetheless, there are some shortcomings with the study – some of which the authors point out themselves, such as that the analysis only includes 2.7% of the events. Others are listed below, hoping that addressing them can improve the study even further. As the authors acknowledge, they could only assess overdiagnosis indirectly, as they investigated CME for treatments (drugs). Given the nature of overDIAGNOSIS one would expect a more elaborate discussion about diagnostic related sponsorship. As primary care physicians were dominating, it should come as no surprise that events were less often held in a clinical setting (hospital or clinic) for all three conditions than other sponsored events.

	There may also be many reasons why the median cost per attendee was higher than for events in general, e.g., geographical and travel related reasons. It is not clear why the sales trends are relevant, as they may be related to many other factors than CME. The relationship between attendees in primary and secondary care may be more related to the selected conditions than to any eager to profit from overdiagnosis. Overall, this is a very interesting study, probably the first of its kind. While it gives new insights, it also has some weaknesses, which may be addressed.

REVIEWER	Adriane Fugh-Berman Georgetown University Medical Center USA I direct PharmedOut, a research and education project at Georgetown University that studies pharmaceutical marketing tactics. I am also a paid expert witness at the request of plaintiffs in litigation regarding pharmaceutical marketing practices.
REVIEW RETURNED	03-Sep-2017

GENERAL COMMENTS	There is scant information in the medical literature regarding industry influence on continuing medical education. This is an excellent study that documents industry sponsorship of “educational” events that target primary care physicians and ply them with food in a successful effort to increase sales for drugs that are not the most cost-effective choices. The study is well-done, important, and can be expected to receive substantial press coverage. I recommend publication. Editing suggestions follow. The title is confusing, and rather boring. I suggest “Industry-sponsored educational events foster overdiagnosis of depression, osteoporosis and overactive bladder syndrome in Australia” . At the very least, please change the incomprehensible “depression, osteoporosis and overactive bladder events”, which evokes fractures and incontinence episodes) Under Results in the abstract, this sentence is confusing: “These condition-focused events included more dinners than other sponsored events, and were more often attended by primary care doctors” What is a “condition-focused” event? What are “other sponsored events”? “More often attended…” than by whom? The conclusions in the abstract are weak. Remember that many people will just read the abstract; it should be a crisp, free-standing summary of the findings, with a strong last line. Instead of “ Industry sponsorship of education on depression, osteoporosis and overactive bladder focused on primary care and was concentrated among few companies that market medicines for each condition. These products are subject to efficacy, safety and cost-effectiveness concerns, raising questions about the focus of sponsored education.” I suggest wording closer to the results in the paper. For example: “This 4-year overview of industry-sponsored events focusing on overdiagnosed conditions found that a few companies sponsored most events, that primary care physicians were the targeted audience, and that meals were often/usually provided. In many cases, products marketed by sponsoring companies were not considered cost-effective choices for the specified conditions.

	This observed pattern of event sponsorship highlights the need for continuing professional education to be free of commercial sponsorship." Please add some information, if available, on what sort of events were company-sponsored. Do these include lunchtime talks, grand rounds, conferences? Page 6 Lines 13-17 Move this sentence: "We report here on event sponsorship with a focus on three conditions highlighted in the medical literature as potentially subject to overdiagnosis: depression, (9) osteoporosis (10), and overactive bladder" to Lines 23-25, after "We also hypothesise that these events tend to target a primary care audience, reflecting milder disease states." Line 44 What does "cleaned the data" mean in this context? And what discrepancies were resolved? Page 8 Line 8 What does "type of hospitality" mean? Line 43 "This was" should be "This included" Page 9 Line 11 "less often" should be "held less often" Line 22 What does "Sponsorship was highly concentrated by company" mean? These are minor suggestions; all in all this is an excellent paper!

REVIEWER	Elissa Ladd MGH Institute of Health Professions I know one of the authors as a professional acquaintance.
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	This was an important study that describes as association between industry sponsored "education" and the companies that market drugs for the noted conditions. It would be useful to be able to identify the content that was included in these educational events, but the authors noted that this information was not available in their limitations. Regarding statistics for the rates of antidepressant use in OECD countries, the United States was not included in this analysis for a reason that is unclear (17). This statement notes that Australia had the second highest rate of antidepressant use among the OECD countries however the US rate during that time frame was 12.7%, so that would position Australia with the third highest rate, but still significant. (Pratt LA, Brody DJ, Gu Q. Antidepressant use among persons aged 12 and over: United States, 2011–2014. NCHS data brief, no 283. Hyattsville, MD: National Center for Health Statistics. 2017.) Finally, in Table 1 Characteristics of sponsored events for the three conditions, in Clinicians present, do you have any identifying information regarding whether the nurses that attended were prescribing nurses, ie nurse practitioners, or were they non-prescribing nurses?

	This would be important to differentiate in order to measure the different clinicians that are targeted by industry. If that information is not available, that might be noted in the limitations.

REVIEWER	Helen K Valier Director, Medicine & Society Program The Honors College University of Houston Houston, TX, 77204-2001 USA
REVIEW RETURNED	27-Sep-2017

GENERAL COMMENTS	I think the paper is interesting and innovative in its selection of data; that it makes a significant (if currently somewhat underdeveloped in this version) contribution to the existing literature on overdiagnosis/overtreatment; and that it is well-written overall. While I do recommend the article for eventual publication I do so with some reservations about the piece in its current form. I believe, however, that only relatively minor revisions would be required to make this paper be of considerable interest to a wide range of readers. My concerns about the current draft version mostly arise from a sense of dissatisfaction with the framing and contextualization of the study rationale. I think the authors could achieve much more with their dataset if they developed a clearer and more confident positioning of the study within the present literature concerning overdiagnosis/overtreatment phenomena and relationships to industry/marketing. A stronger framework/contextual discussion would then allow the authors to draw more substantial, and more interesting, conclusions from their findings than is presently the case. Some points that might make the article stronger in terms of readership/citation/interest: TRANSPARENCY REPORTS. The origins and purpose of the transparency reports used for this research could be better established and this in itself would help the discussion to be of more immediate use and interest to the reader. This need not be a long discussion, a few sentences at most would be sufficient (where did the pressure come from? was there industry opposition? how did all that play out and over what period?) but the reason why such an (internationally) distinctive institutional system was established would be extremely helpful in signposting just what is of general interest and relevance internationally from a public policy and regulation perspective. The authors are concerned with digging into the controversies of overdiagnosis and industry and this is an obvious piece to flesh out in order to start on that pathway. WHAT IS (AND ISN'T) 'AUSTRALIAN' ABOUT THIS STORY? Similar to 1. above, the institutional role of cost-effectiveness is very different between peer countries, from the very strong role of NICE in the UK for instance all the way to the much less central role of USPSTF/AHQR in the US. Where does Australia fall internationally in its institutional oversight (role of PBS, etc)?

	Again, a very helpful to signpost to the uninitiated reader (like myself) on Australian healthcare organization and one that potentially limits international use of and interest in the article. I would also find a definition of what is meant by 'CME' here to be helpful since this is something that differs between different countries. CLARITY OF DESCRIPTION OF DATA SET; HESITANCY TO FULLY EXPLOIT SAME. I found myself rather confused at several points in the article about just what was and was not part of the descriptive part of the initial dataset, specifically over the issue of who, for instance, the attendees were and why they went (something that could be discussed in relation to both the invitation material in the appendix and the literature cited in the article concerning incentives/physician interest). It's all in there it could just be sharper and the more important distinctions drawn more clearly between e.g., specialists versus GPs; clinical vs non-clinical settings, etc. The role of GP prescribing on and off label is an extremely relevant and interesting point that could be pushed much more to make more interesting and important claims so it's something of a missed opportunity to bury that gem right at the end of the discussion on p.13 lines 29-30. The authors do point (appropriately) to the limitations of the data as no names are included and so it is not possible to identify unique attendees (as opposed to repeat attendees) and so on but the data is robust enough to withstand more mining. I feel that the authors are perhaps too hesitant at times to foreground what is really interesting about their data and that's an important thing to do if they want their claim that they are doing something new and of general importance to be taken as credible. To discuss, in another instance, for example, why dinners in particular are of importance is not to overdetermine the data or imply causality in any way but rather to speculate from a sound and transparent basis–and this discussion does come in on pp.12-13 but it needs be polished up and put to the foreground given that the dinners are repeatedly mentioned in the paper but without much in the way of supporting commentary/analysis to why they are a significant/relevant piece of the overall strategies of commercially-driven education. On this latter point I am uncertain on what basis the authors contrast their cases with 'other events in general' as stated several times in the paper. GENERAL COMPARISONS AND WHY THESE STUDIES IN PARTICULAR. It's not particularly clear to me (perhaps more so by the very end of the discussion) how timing influences event-sponsorship, as in when (typically) in the period between initial release and loss of exclusive rights for a particular drug do such events peak? Are there differences? Exceptions? What are links like between such events and larger professional organizations/conferences? It seems the data is there to get into some of these questions at least and these are extremely interesting types of questions that would again make this paper of more substantial interest to a wider readership. Similarly, I found the framing of why these three conditions are discussed in particular to be somewhat underwhelming. This could again be repaired without too much addition to word-count if they were introduced within a contextual discussion of the overdiagnosis literature as it relates to the phenomenon of overintervention or overtreatment (a particular problem in the US where DTC advertising exists not just advertising to doctors).

	OVERDIAGNOSIS/OVERTREATMENT AND THE ROLE OF TECHNOLOGY. A major theme in the existing discussion of overdiagnosis/overtreatment is how technology-driven it is (this is a point nicely-made by the paper cited in [6] in fact) and that's relevant to this paper. The discussion of overactive bladder at p.7 lines 48-49 seems to imply a 'less-than' status of clinical diagnosis as compared to technology-driven diagnosis (and perhaps even a 'suspect' status in that it links to commercially-interested expansion/loosening of diagnostic criteria in order to expand potential patient-population for interventions). If that is indeed what the authors intend to argue then it should be more clearly stated as it is a departure from the standard account (although this account too points to inflated diagnostic criteria it typically does so through links to technology-driven diagnosis which in turn influence more clinical or symptom-based types of diagnosis). DISTINCTION BETWEEN SCREENING TECHNOLOGY AND DIAGNOSTIC TECHNOLOGY. This in relation to the discussion at p.7 lines 41-42. A major part of the discussion of overdiagnosis/overtreatment concerns the role of screening technologies in healthy populations. It's important to note, however, that the same technology can be (often is, in fact) both a screening and a diagnostic tool–a good example of this dual-nature is, for instance, the overuse of the PSA test to screen for prostate cancer as part of routine office visits in asymptomatic patients in the 1990s which lead to a prostate cancer 'epidemic' in the USA; this mass (population-level) use is quite a different type of thing from the use of that very same test at the level of an individual patient (with a determined base-line PSA, etc) in order to monitor the effects of treatment/behavior of tumor: one is a diagnostic tool, one a treatment tool even though they are the same test. For a discussion of this see, for instance, Chapter Six, 'Screening, Patients, and the Politics of Prevention' in Helen Valier, A History of Prostate Cancer: Cancer, Men and Medicine. Palgrave Macmillan, 2016; an excellent general and case-study-based discussion can also be found in Gilbert Welch, Overdiagnosed: Making People Sick in the Pursuit of Health. Beacon Press, 2012. 'PRE'-PATIENTS. The creation of the 'pre-patient' or 'healthy patient'–terms used in the literature and related to points 2. and 3. Above. It is a term used in passing on p.7 line 45 and could use some unpacking. OVERALL CONCLUSION. The statement that education 'needs' to be free of commercial sponsorship is not a conclusion that is well-developed. It is not a particularly realistic goal, at least in the short to medium term. Are there 'third-way' alternatives? If so, what? MINOR THINGS. There is some inconsistency regarding when/where chemical/generic/brand names are used which I found a little distracting. Similarly the difference between regular and extended-release formulae (e.g., Seroquel/Seroquel XR) can be and often is very different in terms of marketing/prescribing patterns and while the authors do not need, I think, to get into those issues in this paper it would be helpful to make it clear that there are differences in formulation that affect prescribing patterns, etc. I would also find it more helpful if more precise language was used when defining the conditions–depression, especially, and perhaps include ICD codes.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Bjorn Hoffman

1. "…there are some shortcomings with the study – some of which the authors point out themselves, such as that the analysis only includes 2.7% of the events."

Response: We agree that this analysis includes only a small proportion of events and have mentioned this limitation [page 13, lines 18-19], which we feel addresses the concern above. However, given the large number of sponsored events over this 4-year period (nearly 117,000), a sample of 2.7% still represents over 3,000 events, a large number in comparison with the medical literature describing industry-sponsored CME to date.

2. As the authors acknowledge they could only assess overdiagnosis indirectly, as they examined CME for treatments (drugs). Given the nature of over DIAGNOSIS one would expect a more elaborate discussion about diagnostic related sponsorship.

Response: This dataset provides limited information on the content of these industry-sponsored events, and many event descriptions are brief and uninformative. See event descriptions in the dataset:
https://researchdata.ands.org.au/pharmaceutical-industry-funded-sept-2015/941218

To examine the extent to which diagnosis is directly discussed in the event descriptions, we carried out an exploratory search for screening or diagnosis using the filter function in Excel and the following terms: diagnos; detect; tests; testing; screen. We identified 1547 events or 1.3% of the total events. Among events focusing on osteoporosis, depression or overactive bladder, 27 events were identified using this search strategy. This was 0.9% of osteoporosis events, 0 depression events, and 7.4% of overactive bladder events. Nearly all descriptions of events focused on the three conditions that include a mention of diagnosis discuss 'diagnosis and treatment' or 'diagnosis and management'.

Given that all three of these conditions have been highlighted in the literature not only as being subject to overdiagnosis but also to overtreatment, and the lack of emphasis on diagnosis in the event descriptions (with the exception of overactive bladder), we felt it was more accurate to focus on overdiagnosis and overtreatment, rather than overdiagnosis alone.

In response to Dr Hoffman's comment, we have therefore shifted the focus of the article to include these two related concepts of overdiagnosis and overtreatment. This is reflected in changes in the title and text.

3. As primary care physicians were dominating, it should come as no surprise that events were less often held in a clinical setting (hospital or clinic) for all three conditions than other sponsored events. There may also be many reasons why the median cost per attendee was higher for events in general, e.g. geographical and travel related reasons.

Response: In general (e.g. for all 116,845 events), if a GP was present, events were held less often in a clinical setting: 34.5% of events, versus 72.1% of events with no GPs present. Clinical settings included GPs' offices, and if a GP was invited to an event outside of their office, this could be in a clinical or a non-clinical setting. Non-clinical settings were typically restaurants, and events involving GPs also included a dinner more often than those at which GPs were not present: 39.2% of events versus 11.1% of events without a GP in attendance.

We also examined whether overseas travel may have been responsible for higher median costs, and in response to this comments, have added explanatory text in the discussion:

We examined whether overseas travel may have been responsible for higher median costs. In total (n=117,845), 1.9% of events were held overseas, and as expected, these events had the highest per person costs. However, only 0.1% of depression-related events, 0.4% of osteoporosis-related events and no overactive bladder events were held overseas. Therefore, this is an unlikely explanation. Travel costs within Australia are not reported separately from other hospitality costs, so we could not examine their contribution to overall costs. [page 14, lines 19-25]

4. It is not clear why sales trends are relevant, as they may be related to many other factors than CME.

Response: We agree that many factors influence sales trends, and that industry-sponsored CME is only one of a large range of promotional activities that may affect sales. We have clarified the lack of established causal relationship in this data set by adding the following line:

A variety of influences are expected to affect sales trends, including a large range of promotional activities. Sponsored events represent only one aspect of broader promotional campaigns to promote sales. (34) [page 13, lines 21-23]

A positive feature of this dataset is the national coverage of sponsored events, which allows comparison with national prescribing trends.

5. The relationship between attendees in primary and secondary care may be more related to the selected conditions than to any eagerness to profit from overdiagnosis.

Response: For all three conditions, a spectrum of severity exists, and treatment at the milder end of the spectrum generally occur in primary care, with more severe cases referred to specialists. We hypothesized that overdiagnosis and overtreatment are more likely to be associated with care at the milder end of the severity spectrum. This is the basis for examining the extent to which these sponsored events have targeted primary versus specialist care clinicians. We agree that we have no data that allows us to know that a specific event was associated with information leading to overdiagnosis or overtreatment. We have added a line stating explicitly that a focus on primary care does not necessarily imply promotion of overdiagnosis. [page 14, lines 6-7]

Reviewer 2: Adriane Fugh-Berman
Thank you for your comments on the quality and importance of the study. We address your editing suggestions below.

1. The title is confusing and rather boring. I suggest “Industry-sponsored educational events foster overdiagnosis of depression, osteoporosis and overactive bladder syndrome in Australia”. At the very least, please change the incomprehensible “depression, osteoporosis and overactive bladder events”, which evokes fractures and incontinence episodes)

Response: Thank you for your suggestion. We have changed the title to:
Does industry-sponsored education foster overdiagnosis and overtreatment of depression, osteoporosis and overactive bladder syndrome? An Australian cohort study

Our data pose a question about the contribution of these events to overdiagnosis rather than allowing a direct claim of causality. We have also added 'overtreatment' in the title to reflect the link to treatment when diagnosis was mentioned (see response to reviewer 1 above).

2. Under Results in the abstract, this sentence is confusing: "These condition-focused events included more dinners than other sponsored events, and were more often attended by primary care doctors" What is a "condition-focused" event? What are "other sponsored events"? "More often attended…" than by whom?

Response: We have changed the wording of the first two sentences in the results section of the abstract, for clarity: Over the study period, we identified 1,567 events focusing on depression, 1,375 on osteoporosis and 190 on overactive bladder (total n= 3,132, with 96,660 attendees). These events were attended by primary care doctors more often than other sponsored events without a focus on these three conditions: relative risk (RR) = 3.06 (95% CI 2.81 – 3.32) for depression, RR= 1.48 (95% CI 1.41-1.55) for osteoporosis, and RR= 2.59 (95% CI 2.09-3.21) for overactive bladder. [page 3, Abstract results]

3. Abstract conclusions – suggestion of stronger wording that provides a crisp, free-standing summary and is closer to the results of the paper.

Response: We have changed the text in the conclusions to the following:

This 4-year overview of industry-sponsored events on three overdiagnosed and overtreated conditions found that primary care clinicians were targeted, dinners often provided, and that a few companies sponsored most events. In most cases, sponsors' products are not cost-effective choices for the specified condition. This pattern highlights the need for professional education to be free of commercial sponsorship. [page 3, Abstract conclusion]

4. Please add some information, if available, on what sort of events were company-sponsored. Do these include lunchtime talks, grand rounds, conferences?

Response: We did not have space in the abstract for this information, but have added it in the introduction.

To answer your question, yes, all of these types of sponsored events were included in the analysis, as well as journal clubs, many dinners at restaurants that included a speaker etc. To clarify the broad range of types of included events, we included the following line in the text:
Over this 4-year period, 116,845 events are described, varying in scope from a half-hour journal club in a hospital meeting room to several-day conferences, sometimes held overseas. (9) [page 6, lines 21-13]

5. Page 6, lines 13-17 Move this sentence: "We report here on event sponsorship with a focus on three conditions highlighted in the medical literature as potentially subject to overdiagnosis: depression, (9) osteoporosis (10), and overactive bladder" to Lines 23-25, after "We also hypothesise that these events tend to target a primary care audience, reflecting milder disease states."

Response: We are suggesting a different solution as we tried moving this sentence as recommended and found the flow of content less intuitive. Instead, we have combined it with the text in the following paragraph as follows:
We report here on event sponsorship with a focus on three conditions highlighted in the medical literature as potentially subject to overdiagnosis and overtreatment: depression, (10) osteoporosis (11), and overactive bladder. (12) We hypothesise that companies marketing drugs for these conditions are more likely to sponsor events with a focus on that condition than other companies. We also hypothesise that these events tend to target a primary care practitioners who are likely to treat milder disease states than specialists. reflecting milder disease states. [page 6, lines 24-29, and page 7, lines 1-2]
6. Line 44 What does “cleaned the data” mean in this context? And what discrepancies were resolved?

The database needed to be prepared for analysis and the data checked for mistakes. For example, for a small minority of events, reported hospitality costs were higher than reported total costs. In these situations, we reported the highest of the two figures as the total cost.

We have added a line explaining this: For example, we removed text from columns that should have contained numeric values only (e.g. total cost) and, for a small minority of events, corrected totals equal to less than reported component costs. [page 7, lines 19-22]

7. Page 8, line 8. What does “type of hospitality” mean?

Response: We have clarified this with an explanatory note. It refers to provision of meals, accommodation and travel. [page 9, lines 11-12]

8. Line 43 “This was” should be “This included”; Page 9, Line 11“less often” should be “held less often”

Response: These have been corrected.

9. What does “Sponsorship was highly concentrated by company” mean?

Response: We have clarified this by rewriting the sentence:
A few companies sponsored most of these condition-focused events. [page 10, line 22]

Reviewer 3: Elissa Ladd

1. In the OECD ‘Health at a glance’ statistics, the United States was not included in this analysis for a reason that was unclear (thank you for noting this).

Response: We agree that Australia likely ranks third after Iceland and the US, and that the prevalence rate of 12.7% in those aged 12 and above is likely higher than Australia’s defined daily dose (DDD) of 96/ 1000. However, the difference in approach to measurement of prevalence makes it difficult to directly compare the Australian and US rates, and we were unable to find a report of US prevalence expressed in defined daily doses. We therefore opted to change the text to state more generally that:
“ In 2013, Australia had one of the highest rates of antidepressant use among OECD countries. (20)”[page 8, line 18-19]

2. Table 1 Characteristics of sponsored events, reports of clinicians present: Were nurses that attended sponsored events prescribing or non-prescribing nurses?

Response: In 2016, only 0.005% of practicing registered nurses in Australia were nurse practitioners, the only type of nurses permitted to prescribe. Therefore, we assumed that the large majority of nurses attending sponsored events were non-prescribing nurses. (Nursing and Midwifery Board of Australia. Registrant Data. Canberra, Australia: Nursing and Midwifery Board of Australia; 2016) A short report in JAMA Internal Medicine, Grundy et al. 2016 ; JAMA Internal Medicine 176 (11): 1718-1719, has provided an overview of the sponsored events attended by nurses. In total, nurse-practitioners were present at less than 1% of events.

An interesting finding is that nurses were less frequently present at events focusing on these three conditions than at other events. We have added a line to state this:

Nurses were only at 24.4% of condition-focused events compared with 39.6% of total events, (12) likely reflecting the less frequent hospital setting. [page 10, lines 12-13]

Reviewer 4: Helen K Valier

1. My concerns about the current draft version mostly arise from a sense of dissatisfaction with the framing and contextualization of the study rationale. I think the authors could achieve much more with their dataset if they developed a clearer and more confident positioning of the study within the present literature concerning overdiagnosis/overtreatment phenomena and relationships to industry/marketing. A stronger framework/contextual discussion would then allow the authors to draw more substantial, and more interesting, conclusions from their findings than is presently the case.

Thank you for this comment. We have looked back at the framing of the text in relation to the literature on overdiagnosis/ overtreatment in relation to industry marketing. One change, noted above, is that we explicitly refer to overtreatment as well as overdiagnosis, which better reflects the data set and the focus of pharmaceutical industry sponsors.

Response: We have added the following section to the introduction:

One consequence of overdiagnosis is overtreatment,as overdiagnosis can expand the pool of potentially treatable patients beyond thresholds at which treatment has been shown to be beneficial. The wide ranging influence of industries that benefit from expanded markets has been highlighted as a key driver. [page 6, lines 1-4]

2. Transparency reports. The origins and purpose of the transparency reports used for this research could be better established: where did the pressure come from? was there industry opposition? how did all that play out and over what period? The reason why such an (internationally) distinctive institutional system was established would be extremely helpful in signposting just what is of general interest and relevance internationally from a public policy and regulation perspective.

Response: We have added some relevant text:

Australia was one of the first countries to require the pharmaceutical industry to publicly report financing of hospitality for health professionals. In 2007, the Australian Competition Tribunal required Medicines Australia – who at the time opposed the move – to introduce mandatory disclosure of industry-sponsored events for health professionals following recommendations by the Australian Competition and Consumer Commission (ACCC). Unlike other countries relying on industry self-regulation of drug promotion via national industry associations, Australia has a what could be described as a quasi-regulatory system, requiring approval of self-regulatory standards by a public regulatory body, the ACCC. (11) [page 6, lines 11-19]

3. What is and isn't Australian about this story? Where does Australia fall internationally in its institutional oversight (role of PBS, etc)? Again, a very helpful to signpost to the uninitiated reader (like myself) on Australian healthcare organization and one that potentially limits international use of and interest in the article.

Response: We have added the following text to explain the role of the PBS in Australia:
The PBS was introduced in 1948 to subsidise the costs of outpatient medicines for the entire Australian population. The aim is to provide affordable access to needed medicines. An expert committee, the Pharmaceutical Benefits Advisory Committee (PBAC) recommends listing of medicines based on cost-effectiveness considerations that include both therapeutic gains and price. Medicines not listed on the PBS tend to have limited sales. [page 7, lines 4-9]

4. I would also find a definition of what is meant by 'CME' here to be helpful since this is something that differs between different countries.

Response: We have added the following line to explain that this is a much broader category than accredited CME: These are described by Medicines Australia as "educational events" and include both accredited CME and a large range of events without accreditation. (10) [page 6, lines 9-10]

10. Clarity of description of the data set; hesitancy to fully exploit same. Confusion about what was and was not part of the descriptive part of the initial dataset (who attendees were; why they went, for example). It's all in there it could just be sharper and the more important distinctions drawn more clearly between e.g., specialists versus GPs; clinical vs non-clinical settings, etc.

Response: This is a secondary analysis of this data set and a detailed analysis has already been published (Fabbri et al. 2017, reference 12). We therefore did not describe these categories in detail, as they have already been described in the primary descriptive article. We have made this relationship more explicit by adding this text:
A descriptive overview of the data on sponsored events has been published, (9) and the data set used for this analysis is available at: https://researchdata.ands.org.au/pharmaceutical-industry-funded-sept-2015/941218 [pages 7, line 26, and page 8, lines 1-2]

11. The role of GP prescribing on and off label is an extremely relevant and interesting point that could be pushed much more to make more interesting and important claims so it's something of a missed opportunity to bury that gem right at the end of the discussion on p.13 lines 29-30.

Response: We agree with the importance of this issue and its relevant to this analysis. However, in this data set, we could not directly assess the extent of off-label prescribing, or of education that directly promotes off-label prescribing given the concise and limited descriptions of events.

12. I feel that the authors are perhaps too hesitant at times to foreground what is really interesting about their data and that's an important thing to do if they want their claim that they are doing something new and of general importance to be taken as credible. To discuss, in another instance, for example, why dinners in particular are of importance is not to overdetermine the data or imply causality in any way but rather to speculate from a sound and transparent basis–and this discussion does come in on pp.12-13 but it needs be polished up and put to the foreground given that the dinners are repeatedly mentioned in the paper but without much in the way of supporting commentary/analysis to why they are a significant/relevant piece of the overall strategies of commercially-driven education.

Response: We added text on why we had focused on dinners in the introduction:
We examined how often events included company-sponsored dinners as events with dinners provided are often held at a restaurant and represent a higher-value gift. [page 7, lines 11-13]

13. On this latter point I am uncertain on what basis the authors contrast their cases with 'other events in general' as stated several times in the paper.

Response: This focus is now explained in the Introduction, in the discussion of testing of key study hypotheses:
We hypothesise that companies marketing drugs for these conditions are more likely to sponsor events with a focus on that condition than other companies. We also hypothesise that these events tend to target primary care practitioners, who are likely to treat milder disease states than specialists. To test these hypotheses, we compare characteristics of the events focusing on these three conditions with other events sponsored by companies during the 4-year study period. [page 6, lines 26-29, page 7, lines 1-2]

14. It's not particularly clear to me (perhaps more so by the very end of the discussion) how timing influences event-sponsorship, as in when (typically) in the period between initial release and loss of exclusive rights for a particular drug do such events peak? Are there differences? Exceptions? What are links like between such events and larger professional organizations/conferences? It seems the data is there to get into some of these questions at least and these are extremely interesting types of questions that would again make this paper of more substantial interest to a wider readership.

Response: We have clarified in the Introduction that we only looked at timing in relation to when a company held distribution rights for a specific product, if there were shifts in distribution rights over the study period. In these cases, we examined whether these shifts were accompanied by a shift in sponsorship patterns. This involved only a few relevant products for which, over the study period, there was a change in which company held distribution rights.

Changed text: For products for which there was a shift in which company held distribution rights over the study period, we also examined timing of event sponsorship in relation to distribution rights. [page 7, lines 13-14]

15. Similarly, I found the framing of why these three conditions are discussed in particular to be somewhat underwhelming. This could again be repaired without too much addition to word-count if they were introduced within a contextual discussion of the overdiagnosis literature as it relates to the phenomenon of overintervention or overtreatment (a particular problem in the US where DTC advertising exists not just advertising to doctors).

Response: We have added the following text below the descriptions of the three conditions:
Drug treatments for these three conditions have been heavily advertised to the public in the United States (US), with advertising that relies heavily on emotional appeals, targets women, and tends to blur the boundaries between normal life and medical conditions requiring treatment. (22) [page 9, lines 6-8]

16. OVERDIAGNOSIS/OVERTREATMENT AND THE ROLE OF TECHNOLOGY. A major theme in the existing discussion of overdiagnosis/overtreatment is how technology-driven it is (this is a point nicely-made by the paper cited in [6] in fact) and that's relevant to this paper. The discussion of overactive bladder at p.7 lines 48-49 seems to imply a 'less-than' status of clinical diagnosis as compared to technology-driven diagnosis (and perhaps even a 'suspect' status in that it links to commercially-interested expansion/loosening of diagnostic criteria in order to expand potential patient-population for interventions). If that is indeed what the authors intend to argue then it should be more clearly stated as it is a departure from the standard account (although this account too points to inflated diagnostic criteria it typically does so through links to technology-driven diagnosis which in turn influence more clinical or symptom-based types of diagnosis).

Response: Of the three conditions under discussion, only one is strongly technology driven, osteoporosis. We have added text to more explicitly state this:

Questions have also been raised about diagnostic criteria for osteoporosis and the role of bone densitometry in greatly expanding the treatable population, primarily when used in screening of asymptomatic post-menopausal women, but also as a diagnostic tool for women with low trauma fractures. [page 8, lines 20-23]

17. DISTINCTION BETWEEN SCREENING TECHNOLOGY AND DIAGNOSTIC TECHNOLOGY. This in relation to the discussion at p.7 lines 41-42. A major part of the discussion of overdiagnosis/overtreatment concerns the role of screening technologies in healthy populations. It's important to note, however, that the same technology can be (often is, in fact) both a screening and a diagnostic tool–a good example of this dual-nature is, for instance, the overuse of the PSA test to screen for prostate cancer as part of routine office visits in asymptomatic patients in the 1990s which lead to a prostate cancer 'epidemic' in the USA; this mass (population-level) use is quite a different type of thing from the use of that very same test at the level of an individual patient (with a determined base-line PSA, etc) in order to monitor the effects of treatment/behavior of tumor: one is a diagnostic tool, one a treatment tool even though they are the same test. For a discussion of this see, for instance, Chapter Six, 'Screening, Patients, and the Politics of Prevention' in Helen Valier, A History of Prostate Cancer: Cancer, Men and Medicine. Palgrave Macmillan, 2016; an excellent general and case-study-based discussion can also be found in Gilbert Welch, Overdiagnosed: Making People Sick in the Pursuit of Health. Beacon Press, 2012.

Response: See change to text above – we agree that this is an important distinction.

18. PRE'-PATIENTS. The creation of the 'pre-patient' or 'healthy patient'–terms used in the literature and related to points 2. and 3. Above. It is a term used in passing on p.7 line 45 and could use some unpacking.

Response: We have elaborated this point further:
Further treatment expansion has occurred through lowered thresholds for "pre-osteoporosis" and "osteopenia", which further extend disease labelling to populations that fail to meet established criteria for a diagnosis of osteoporosis. [page 8, lines 24-27]

19. OVERALL CONCLUSION. The statement that education 'needs' to be free of commercial sponsorship is not a conclusion that is well-developed. It is not a particularly realistic goal, at least in the short to medium term. Are there 'third-way' alternatives? If so, what?

Response: We have changed the wording slightly to reflect the concern raised above:
This observed pattern of event sponsorship raises concerns about the role of industry-sponsored education in conditions identified as prone to overdiagnosis, and highlights the need for ensure that professionals have ready access to continuing professional education that is free of commercial sponsorship. [page 15, lines 10-13]
However, we disagree with the suggestion that ensuring education is free of commercial sponsorship is an unrealistic goal, as some medical faculties in the U.S. have already introduced policies to prohibit industry-sponsored CME. See for example:

Hutchinson RJ, U-M Medical School plans changes to Continuing Medical Education funding. Available at http://www.uofmhealth.org/u-m-medical-school-plans-changes-continuing-medical-education-funding

Smith SR, Policy Guide for Academic Medical Centers and Medical Schools. Toolkit on Continuing Medical Education. Available at http://www.communitycatalyst.org/doc-store/publications/CME_toolkit.pdf

20. There is some inconsistency regarding when/where chemical/generic/brand names are used which I found a little distracting. Similarly the difference between regular and extended-release formulae (e.g., Seroquel/Seroquel XR) can be and often is very different in terms of marketing/prescribing patterns and while the authors do not need, I think, to get into those issues in this paper it would be helpful to make it clear that there are differences in formulation that affect prescribing patterns, etc.

Response: We have corrected the text to include the generic name only, except the first time that extended-release quetiapine is introduced, as mention of the brand name helps to clarify which quetiapine formulation is under discussion. We have also specified that the extended release formulation of quetiapine is the only formulation approved for depression and anxiety diagnoses.

21. I would also find it more helpful if more precise language was used when defining the conditions–depression, especially, and perhaps include ICD codes.

Response: The nature of the data set makes it difficult to assign ICD codes and impose a precise definition for these conditions. The references in the data set were varied and in some cases very general. For example, the AstraZeneca events focusing on 'the anxious, depressed patient' and others on 'difficult to treat depression' may span a range of ICD codes within F30-F39 (but clearly not all of the codes). Others focused on depression in diabetes, renal or cardiovascular patients. Some events described "the anxiety spectrum; and current understandings".

We have listed the coding terms we used in the on-line appendix, and also provide access to the database of listed events, in order to provide more information on definitions of these conditions.

VERSION 2 – REVIEW

REVIEWER	Bjørn Hofmann NTNU and University of Oslo Norway
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	The comments and suggestions have been addressed in an appropriate manner.

REVIEWER	Elissa Ladd MGH Institute of Health Professions
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	The authors addressed all questions/concerns/suggestions from the reviewers fully.

REVIEWER	Helen Valier, PhD The Medicine & Society Program The Honors College at the University of Houston Houston, Texas, USA
REVIEW RETURNED	10-Nov-2017

GENERAL COMMENTS	The authors have done a good job in responding to reviewer comments and have incorporated them appropriately. As such my earlier concerns re framing and context (overtreatment/overdiagnosis); clarity of writing in places; what was uniquely or interestingly 'Australian' about this story, etc are all now satisfied; I am happy to recommend the manuscript for publication without a need for further revision.