

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

TITLE (PROVISIONAL)	A cross-sectional analysis of pharmaceutical industry-funded events for health professionals in Australia
AUTHORS	Fabbri, Alice; Grundy, Quinn; Mintzes, Barbara; Swandari, Swestika; Moynihan, Ray; Walkom, Emily; Bero, Lisa

VERSION 1 - REVIEW

REVIEWER	A/Prof Geoffrey Smith Western Australian Centre for Mental Health Policy Research, Department of Health Western Australia, Australia
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	<p>This study, which analyses the sponsorship of educational events for health professionals by the pharmaceutical industry (PI) in Australia over a four year period, makes an important contribution in an area that is of major concern to government internationally. As the authors point out, this study is the first to make use of the extensive available Australian data. The creation of an 'accessible' open-access searchable database for researchers adds another important dimension.</p> <p>The paper is well written and accessible to readers. It provides a good overview of the pervasive nature of the relationship between the PI and health professionals (and importantly trainees) and the potential implications of this relationship.</p> <p>The implications of the study's findings are well dealt with, including 1) recognition of the potential responsibility of hospitals in the 'transparency' process (and I would add universities and professional associations) and 2) the longer-term need to address the 'independent' funding of continuing professional development for health professionals.</p> <p>Given that this paper is addressing transparency provisions in Australia for an international audience, it could be improved by clearer contextualisation of the Australian system. US, for example, has legislated for transparency, while Australia has taken a different route with industry self-regulation through a Code of Conduct (albeit that the ACCC has a role in 'approving', but not 'determining' the elements of the Code). The authors make reference to the changes to the Code, with a new Code (version 18) introduced in October 2015. Given that this study is of the financial relationship between the PI and health professionals under the provisions of the earlier Codes (aggregate reporting), it may be useful to briefly outline the changes to the code (individual reporting) to put the current study in contemporary Australian context.</p>
-------------------------	--

	Overall, a very useful paper that adds to the international research base. I would recommend it for publication - with or without the minor changes suggested above.
--	--

REVIEWER	Frieder Keller University Hospital ulm, gernamy
REVIEW RETURNED	22-Mar-2017

GENERAL COMMENTS	<p>General</p> <p>Physicians want to be independent. But they dislike transparency that could do harm to their reputation and integrity. On the other side, physicians do more for life-long learning than probably any other profession. Thus, a feeling could grow to be disadvantaged making them susceptible to the honoraria and acknowledgements offered by the pharmaceutical industry. Only full transparency will enable the peer professionals and the public to judge on whether the funding by industry is adequate or corrupting. The study by Alice Fabbri shows that the incentives are only modest (line 237). But the intention to disregard funding for meals and drinks makes transparency declarations just disregard the main field of sponsoring.</p> <p>Suggestions</p> <ol style="list-style-type: none"> 1. The honoraria for speakers should be clearly separated from the food and drink sponsoring. The honoraria for the speakers can be inadequate and too high while the sponsoring of the audiences is frugal ... 2. It is a big disadvantage of the study that only electronic data are analyzed but no empiric validation is done. Why not look after some meetings, workshops, journal clubs on whether the recorded data are in agreement with reality ? <p>Special</p> <p>Line 31: Make more clear the potential impact on the intended changes of new regulations.</p> <p>Line 43: Why is an event in the hospital more pervasive than in a restaurant ... the reverse might be true.</p> <p>Line 167: The quartiles Q2 and Q3 might be more useful than the standard deviation.</p> <p>Line 197: What does it mean when the scientific meetings are more expensive ... ?</p> <p>Lines 230 – 234: The numbers might indicate that nearly every medical professional (0.7 physicians per year) might be attending an industry sponsored meeting within one year.</p> <p>References: reference 6 possibly is incompletely cited ...</p> <p>Line 392 and following. It is not clear whether there was any honorarium received by one of the authors from a company or not. Many words no facts.</p> <p>Table 1: Make it more clear what is speaker fee and what hospitality ? The latter might be OK but the other too high ... ?</p> <p>Table 2: Give figures for all areas not only three.</p> <p>Supplementary file 1: most of that is trivial.</p>
-------------------------	---

REVIEWER	<p>Cinzia Colombo IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy</p> <p>I had an exchange of opinions about COI with the main author of this paper and I am currently discussing possible future collaborations with a co-author. I do not perceive these as intellectual conflicts of</p>
-----------------	---

	interest.
REVIEW RETURNED	23-Mar-2017

GENERAL COMMENTS	<p>The article by Fabbri et al. provides an interesting and timely analysis that shows the possible consequences of excluding pharmaceutical companies' funding of food and beverage from disclosure codes or legislations. Furthermore, the availability of an open access searchable database on events funded by pharmaceutical industries is a great step towards more transparency.</p> <p>As acknowledged in the article, the reports analysed belong to a group of pharmaceutical companies and do not cover the total number of pharmaceutical companies based in Australia, so the findings could underestimate the extent of funding for events aimed at health professionals.</p> <p>All this considering, and in order to increase the clarity of some parts of the article, minor revisions are required.</p> <p>In particular:</p> <ul style="list-style-type: none"> -In the introduction and in the discussion, the authors refer to disclosure policies being debated and revised in several settings: adding references to the international codes and legislations to which the authors refer would be useful for the reader. -It would be also useful adding a clear definition of "event" - explaining how it relates to the medical education of health professionals - and clarifying if the Medicines Australia's code covers also events funded by pharmaceutical companies but formally organized and promoted by communication agencies. - The objective reported in the introduction ("describe the nature and frequency of industry-sponsored events for health professional") has to be modified in order to better comply with the methods and limits (analysis of public reports produced by the Australian pharmaceutical companies members of Medicines Australia): see the objective reported in the abstract. -Regarding the coding scheme and the keywords used for the analysis: which variables were in the reports of the pharmaceutical companies? How were defined the variables of theoretical interest, the coding scheme and the keywords? The authors should provide more details on this. -As underlined both in the methods and in the discussion sections, this study deals with reports submitted voluntarily by companies to Medicine Australia, excluding other companies (not members of Medicine Australia; manufacturers of generic medicine, over the counter medicine and devices). It would be interesting to know how many companies are based in Australia, at least manufacturers of prescription medicines, as a frame of reference for the findings. -In the discussion, the statement "the findings show decision-makers the extent of the "free food" paid by companies" has to be modified in order to better comply with the limitations of the study. <p>In the discussion, the authors should explain better two topics briefly presented:</p>
-------------------------	---

	<p>- the authors say that ways of expanding funding for independent continuing professional education should be explored: who should explore them, and how? Are there experiences available, or legislations considered better than others?</p> <p>- the authors say that health professionals should be more aware of the independent sources of information on drugs already available: is this a call aimed at health professionals? Is it a suggestion for public health agencies to boost independent sources within the education of health professionals? This point should be clarified.</p>
--	--

REVIEWER	Agnes Vitry University of South Australia
REVIEW RETURNED	26-Mar-2017

GENERAL COMMENTS	<p>This is very interesting and much needed research paper as the results may be used for developing appropriate policies on reporting of funding of health professionals by pharmaceutical companies.</p> <p>I have only two minor comments</p> <p>The abstract mentions that 82% medical doctors attended events, however medical doctors are not mentioned in the core article, it would be good to clarify whether medical doctors include the two categories 'medical specialist' and 'primary care doctors' displayed in Table 2.</p> <p>The text mentions that 'otolaryngology' and 'andrology' were least represented, it would be nice to have all the clinical areas of focus included in Table 2 or in a supplementary table.</p>
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: A/Prof Geoffrey Smith

Institution and Country: Western Australian Centre for Mental Health Policy Research, Department of Health Western Australia, Australia

Please state any competing interests: None declared

This study, which analyses the sponsorship of educational events for health professionals by the pharmaceutical industry (PI) in Australia over a four year period, makes an important contribution in an area that is of major concern to government internationally. As the authors point out, this study is the first to make use of the extensive available Australian data. The creation of an 'accessible' open-access searchable database for researchers adds another important dimension.

The paper is well written and accessible to readers. It provides a good overview of the pervasive nature of the relationship between the PI and health professionals (and importantly trainees) and the potential implications of this relationship.

The implications of the study's findings are well dealt with, including 1) recognition of the potential responsibility of hospitals in the 'transparency' process (and I would add universities and professional associations) and 2) the longer-term need to address the 'independent' funding of continuing professional development for health professionals.

RESPONSE: We thank the reviewer for these positive comments. Following his suggestion, we amended the sentence on the potential responsibilities of hospitals in the transparency process to include universities and professional associations (line 308, page 12).

Given that this paper is addressing transparency provisions in Australia for an international audience, it could be improved by clearer contextualisation of the Australian system. US, for example, has legislated for transparency, while Australia has taken a different route with industry self-regulation through a Code of Conduct (albeit that the ACCC has a role in 'approving', but not 'determining' the elements of the Code). The authors make reference to the changes to the Code, with a new Code (version 18) introduced in October 2015. Given that this study is of the financial relationship between the PI and health professionals under the provisions of the earlier Codes (aggregate reporting), it may be useful to briefly outline the changes to the code (individual reporting) to put the current study in contemporary Australian context.

Overall, a very useful paper that adds to the international research base. I would recommend it for publication - with or without the minor changes suggested above.

RESPONSE: The second paragraph of the Introduction (line 85-99, page 4) describes the Australian transparency provisions and the recently implemented changes. As the reviewer notes, the ACCC has played an important role, we describe its involvement in the process and provide a reference for that (Reference 6). Following the reviewer's suggestion, we have added additional details on the recent changes to the Code (lines 96-99, page 4).

Reviewer: 2

Reviewer Name: Frieder Keller

Institution and Country: University Hospital ulm, gernamy

Please state any competing interests: no conflict

General

Physicians want to be independent. But they dislike transparency that could do harm to their reputation and integrity. On the other side, physicians do more for life-long learning than probably any other profession. Thus, a feeling could grow to be disadvantaged making them susceptible to the honoraria and acknowledgements offered by the pharmaceutical industry. Only full transparency will enable the peer professionals and the public to judge on whether the funding by industry is adequate or corrupting. The study by Alice Fabbri shows that the incentives are only modest (line 237). But the intention to disregard funding for meals and drinks makes transparency declarations just disregard the main field of sponsoring.

Suggestions

1. The honoraria for speakers should be clearly separated from the food and drink sponsoring. The honoraria for the speakers can be inadequate and too high while the sponsoring of the audiences is frugal.

RESPONSE: The reviewer raises an interesting point, however as noted in the Discussion (lines 303-307, page 12), we think that transparency rules should be as inclusive as possible regardless of the value of the payment. There is indeed considerable evidence that free food and drink may influence medical practice. As Reference 15 of the manuscript shows, a study involving data from almost

280,000 physicians in the United States found that even the provision of low cost meals is associated with increased prescribing of promoted, costly, brand-name medications. In light of growing evidence that food and beverage correlate strongly with increased prescribing, we believe that our findings of frequent sponsored meals are quite timely and underscore the need for more disclosure regardless of the value of the gifts.

Moreover, it was not possible for us to clearly separate the honoraria for speakers from the provision of food and drinks due to inconsistencies between companies in reporting. For example, while some companies provided a total cost for an event in aggregate, others reported separately by room rentals/speaker fees/other expenses.

2. It is a big disadvantage of the study that only electronic data are analyzed but no empiric validation is done. Why not look after some meetings, workshops, journal clubs on whether the recorded data are in agreement with reality?

RESPONSE: This is a key limitation of our analysis and we have highlighted this in the “Strengths and Limitations.” We did not verify the accuracy or completeness of the reports, but instead relied upon the data as presented by companies and made available by Medicines Australia. However, we agree that this is an important topic for future research and believe our analysis provides the groundwork for prospective and comparative study of industry-sponsored events. Furthermore, it is unclear whether a data source for validation can be obtained. For example, journal clubs do not typically report their fundings sources and meetings often report sponsors only, but not the amount and category of funding by sponsor.

Special

Line 31: Make more clear the potential impact on the intended changes of new regulations.

RESPONSE: We have amended the abstract to reflect more specifically the key impact of the intended changes, namely the omission of reporting of food and beverages (lines 29-30, page 2).

Line 43: Why is an event in the hospital more pervasive than in a restaurant ... the reverse might be true.

RESPONSE: The purpose of that sentence (line 47, page 2) was not to underplay the role of events held in restaurants or other venues. We were commenting on the relative frequency of events, and not on their influence on health professionals which would be beyond what this data can show. Since almost two thirds of the events in our sample were held in a clinical setting, we commented only on the pervasive presence of pharmaceutical companies in that setting.

Line 167: The quartiles Q2 and Q3 might be more useful than the standard deviation.

RESPONSE: Following the reviewer’s suggestion, we replaced the mean and standard deviation with median and interquartile range (line 177, page 8).

Line 197: What does it mean when the scientific meetings are more expensive ... ?

RESPONSE: As Supplementary File 1 shows, the keywords we used to code for “scientific meetings”

include “congress”, “conference” and it is highly likely that these larger and more diverse events have higher costs compared to other event types such as journal clubs, workshops, and internal meetings. We have clarified the nature of “scientific meetings” on page 9, line 208. However, only 4.2% of the events in our sample were described as scientific meetings. As we note in the first paragraph of the Discussion, it seems therefore that the more modest sponsored events held in the clinical setting are the principal form of contact between industry and health professionals.

Lines 230 – 234: The numbers might indicate that nearly every medical professional (0.7 physicians per year) might be attending an industry sponsored meeting within one year.

RESPONSE: In the first paragraph of the Discussion, we provide a frame of reference to compare the number of registered health professionals in Australia with the number of individual attendances at sponsored events. As the reviewer notes, these numbers could indicate that nearly every health professional could be attending an industry sponsored meeting each year. However, because the number of attendees was reported in aggregate and individuals were not named, we could not ascertain numbers of repeat attendees.

References: reference 6 possibly is incompletely cited.

RESPONSE: The Reference is now correctly cited.

Line 392 and following. It is not clear whether there was any honorarium received by one of the authors from a company or not. Many words no facts.

RESPONSE: We have simplified the statement (line 430, page 16) and added the additional clarifying sentence: “None of the authors received any payments, funding or other financial support from pharmaceutical manufacturers.”

Table 1: Make it more clear what is speaker fee and what hospitality ? The latter might be OK but the other too high ... ?

RESPONSE: We prepared Table 1 with examples taken largely verbatim from the transparency reports in order to provide illustrative case studies, but including our calculations of the costs of hospitality per head. We provided this Table to give readers a sense of the nature of the reports and data available, and to give an appreciation of the wide range of hospitality costs per head. In light of the reviewer’s question, we have decided to revise the Table, and now include precisely the verbatim text extracted from the original company reports, without any of our additional calculations, to offer readers an insight into the exact nature of the data provided in the original reports. Thus, for some examples this may provide some clarity about what components of the total cost are speakers fees and what components hospitality, though, as noted in our limitations section (line 286, page 11) there is no standardisation in the way all the figures are presented across all events and all company reports. We have added a footnote to the Table to explain that the data in the table was extracted verbatim from the original company reports.

Table 2: Give figures for all areas not only three.

RESPONSE: Following the reviewer’s suggestion, the complete list of the clinical areas has been added to Table 2.

Supplementary file 1: most of that is trivial.

RESPONSE: We believe that sharing the complete coding scheme is important for the sake of transparency and also for potential additional analyses of the database.

Reviewer: 3

Reviewer Name: Cinzia Colombo

Institution and Country: IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Please state any competing interests: I had an exchange of opinions about COI with the main author of this paper and I am currently discussing possible future collaborations with a co-author. I do not perceive these as intellectual conflicts of interest.

The article by Fabbri et al. provides an interesting and timely analysis that shows the possible consequences of excluding pharmaceutical companies' funding of food and beverage from disclosure codes or legislations. Furthermore, the availability of an open access searchable database on events funded by pharmaceutical industries is a great step towards more transparency.

RESPONSE: We thank the reviewer for these positive comments.

As acknowledged in the article, the reports analysed belong to a group of pharmaceutical companies and do not cover the total number of pharmaceutical companies based in Australia, so the findings could underestimate the extent of funding for events aimed at health professionals. All this considering, and in order to increase the clarity of some parts of the article, minor revisions are required.

In particular:

-In the introduction and in the discussion, the authors refer to disclosure policies being debated and revised in several settings: adding references to the international codes and legislations to which the authors refer would be useful for the reader.

RESPONSE: The sentence on the disclosure policies being debated and revised (line 101, page 5) refers to the codes and legislations mentioned in the first two paragraphs of the Introduction, namely the recently implemented EFPIA Disclosure Code (Reference 1), the recently implemented Medicines Australia Code (Reference 3), and the US bill that would exempt pharmaceutical companies from reporting payments related to continuing medical education.(Reference 2). They have now been added as a reference to that sentence.

-It would be also useful adding a clear definition of "event" - explaining how it relates to the medical education of health professionals - and clarifying if the Medicines Australia's code covers also events funded by pharmaceutical companies but formally organized and promoted by communication agencies.

RESPONSE: The 17th edition of the Medicines Australia Code (available at: <http://medicinesaustralia.com.au/files/2010/01/20120702-Edition17-FINAL.pdf>) states that member companies should provide a report on "all educational meetings and symposia as defined in Section 9

of the Code held or sponsored by that company". This mainly includes:

- company initiated events held in Australia, namely events where "the company typically initiates and manages the duration of educational content and the selection of the speakers" (Section 9.4);
- sponsored educational events, namely "events which are organised by a society, college, university or other healthcare professional organisation". In this case "the third party organising the educational meeting should independently determine the educational content, select the speakers and invite the attendees. (...)The sponsoring company may propose a speaker for the educational meeting, but the final choice of speakers will be determined by the healthcare professional organisation or nominated faculty". (Section 9.5);
- trade displays (section 9.6);
- sponsorship of healthcare professionals to attend educational events - Australasian and international (section 9.7)

A clarification on what the transparency reports cover has been added to the Introduction (lines 88-90, page 4).

The objective reported in the introduction ("describe the nature and frequency of industry-sponsored events for health professional") has to be modified in order to better comply with the methods and limits (analysis of public reports produced by the Australian pharmaceutical companies members of Medicines Australia): see the objective reported in the abstract.

RESPONSE: Following the reviewer's suggestion, we have amended the first objective reported in the Introduction (line 109, page 5) to state: "The objectives of this study are: to describe the nature and frequency of events for health professionals sponsored by pharmaceutical companies that are members of Medicines Australia." We have also stressed this limitation in the "Strengths and Limitations" section (lines 66-69, page 3).

-Regarding the coding scheme and the keywords used for the analysis: which variables were in the reports of the pharmaceutical companies? How were defined the variables of theoretical interest, the coding scheme and the keywords? The authors should provide more details on this.

RESPONSE: The variables included in the original reports are now more clearly listed in the Methods (lines 126-128, page 5).

The Methods section has also been amended to clarify that the coding scheme was based on the available literature on industry-health professional interactions, on two previous analyses of data from the first six months of the Australian disclosure scheme (References 4 and 7), and on iterative searches of the unstructured text conducted by several members of the research team. (line 132-144, page 6).

-As underlined both in the methods and in the discussion sections, this study deals with reports submitted voluntarily by companies to Medicine Australia, excluding other companies (not members of Medicine Australia; manufacturers of generic medicine, over the counter medicine and devices). It would be interesting to know how many companies are based in Australia, at least manufacturers of prescription medicines, as a frame of reference for the findings.

RESPONSE: According to the Department of Industry, Innovation and Science of the Australian Government, there are approximately 140 separate firms listed as suppliers to the Australian Pharmaceutical Benefit Scheme (PBS). The PBS Schedule of Pharmaceutical Benefits lists all drugs that are eligible for public subsidy. This information has been added to the Discussion (line 278-280, page 11).

-In the discussion, the statement “the findings show decision-makers the extent of the “free food” paid by companies” has to be modified in order to better comply with the limitations of the study.

RESPONSE: Following the reviewer’s suggestion, we have amended the last paragraph of the manuscript. We clarified that this analysis underestimates the extent of industry sponsorship of events for health professionals and highlighted that the policy implication of our study is that exclusion of common (and underestimated) payments will decrease transparency. (lines 323-328, page 12)

In the discussion, the authors should explain better two topics briefly presented:

- the authors say that ways of expanding funding for independent continuing professional education should be explored: who should explore them, and how? Are there experiences available, or legislations considered better than others?

RESPONSE: Following the reviewer’s suggestion, we have expanded that section providing examples of institutions that have already moved away from dependence on pharmaceutical industry funding for their educational events. (line 314-317, page 12)

- the authors say that health professionals should be more aware of the independent sources of information on drugs already available: is this a call aimed at health professionals? Is it a suggestion for public health agencies to boost independent sources within the education of health professionals? This point should be clarified.

RESPONSE: We have clarified that universities and professional societies should promote awareness of these independent sources of information. (line 318, page 12)

Reviewer: 4

Reviewer Name: Agnes Vitry

Institution and Country: University of South Australia

Please state any competing interests: 'None declared'

This is very interesting and much needed research paper as the results may be used for developing appropriate policies on reporting of funding of health professionals by pharmaceutical companies.

RESPONSE: We thank the reviewer for her comments.

I have only two minor comments

The abstract mentions that 82% medical doctors attended events, however medical doctors are not mentioned in the core article, it would be good to clarify whether medical doctors include the two categories ‘medical specialist’ and ‘primary care doctors’ displayed in Table 2.

RESPONSE: A clarification has been added to the abstract to indicate that medical doctors comprises both specialists and primary care doctors (line 40, page 2).

The text mentions that ‘otolaryngology’ and ‘andrology’ were least represented, it would be nice to

have all the clinical areas of focus included in Table 2 or in a supplementary table.

RESPONSE: The complete list of the clinical areas of focus have been added to Table 2.

VERSION 2 – REVIEW

REVIEWER	Assoc/Prof Geoffrey Smith WA Centre for Mental Health Policy Research, Department of Health, Western Australia, Australia
REVIEW RETURNED	16-Apr-2017

GENERAL COMMENTS	The authors have addressed almost all the comments raised by the reviewers to my satisfaction. The only amendment that I would suggest - and that is a very minor one - is that they clarify early, preferably in the INTRODUCTION (rather than on page 11) that the transparency provisions (and therefore their study) cover only the companies (42, out of the 140) that are members of Medicines Australia. They make adequate reference to this in the limitations section of their paper, but it would be useful to see it set out clearly at the outset.
-------------------------	---

REVIEWER	Frieder Keller Nephrology, Department of Internal Medicine 1, University Hospital, Ulm, Germany
REVIEW RETURNED	14-Apr-2017

GENERAL COMMENTS	OK
-------------------------	----

REVIEWER	Cinzia Colombo IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy I had an exchange of opinions about COI with the main author of this paper and I am currently discussing future collaborations with a co-author. I do not perceive these as intellectual conflicts of interest.
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	The authors have satisfactorily addressed all comments.
-------------------------	---

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Reviewer Name: Assoc/Prof Geoffrey Smith

Institution and Country: WA Centre for Mental Health Policy Research, Department of Health, Western Australia, Australia

Please state any competing interests: Non declared

The authors have addressed almost all the comments raised by the reviewers to my satisfaction. The only amendment that I would suggest - and that is a very minor one - is that they clarify early, preferably in the INTRODUCTION (rather than on page 11) that the transparency provisions (and therefore their study) cover only the companies (42, out of the 140) that are members of Medicines

Australia. They make adequate reference to this in the limitations section of their paper, but it would be useful to see it set out clearly at the outset.

RESPONSE: We have noted that the study only covers members of Medicines Australia in the Strengths and Limitations section (line 66, page 3), and in the Introduction (line 87, page 4 and line 109, page 5). Following the reviewer's suggestion, we included greater detail on the proportion of companies that are members earlier in the paper. On page 6 (line 130-134), in the Methods section, we clarified the number of companies issuing transparency reports, and the process of grouping companies based on mergers and acquisitions to arrive at our sample of 42. We have also noted the proportion of Australian pharmaceutical companies that member companies comprise in the Methods section as a frame of reference.