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)	Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the United States with Different Regulatory Controls: a Cross-Sectional Study
AUTHORS	Diep, Dion; Mosleh-Shirazi, Abnoos; Lexchin, Joel

VERSION 1 - REVIEW

REVIEWER	Shai Mulinari Lund University, Sweden
REVIEW RETURNED	07-Nov-2019

GENERAL COMMENTS	Thank you for the opportunity to review "Comparison of the Quality of Journal Advertisements Produced Under Different Forms of Regulation: A Cross Sectional Study". This is an interesting, well-researched and well-written paper that I think ultimately should be published. However, I have a few comments and questions to the authors which I list below. 1. My main concern pertains to the key claim that observed differences in ad quality must reflect differences in the regulation of drug promotion e.g. in Abstract conclusion. It's clear that this is one possibility, but couldn't differences (also) be caused by various other regulatory, legal, cultural or health system factors that differ between countries and that cannot easily be controlled for in this study. For example, could the fact that US ads more often contain warnings/contraindications, and give more prominence to safety information, reflect industry concerns with litigation rather than FDA regulation per se. Could some differences (e.g. reference to surrogate endpoints) reflect differences in labelling rather than drug promotion oversight? And what about differences in journal ad polices? Etc. 2. Related to the previous point, I think the argument about the causal link to drug advertising regulation would become more compelling if the authors present one or more putative mechanisms that could explain differences. One problem, however, that I see here is that some of the criterion that are being evaluated, although pertinent to drug prescribing, might not be considered relevant criterion to drug promotion regulators. Still, the paper's argument would be stronger if the authors could show that low quality ads either violate regulations/industry codes (suggesting weaker oversight in Australia/Canada) or that FDA regulations are more demanding (suggesting weaker rules in Australia/Canada), or both. 3. Further to this point, the authors argue in the Discussion that their study show that the US government has failed to adequately control

	journal advertising, possibly due to limited resources, but in the Limitation section they acknowledged that the study has not considered if ads conformed to regulatory requirements. 4. It is stated that this study "is the first to examine information in ads that may affect prescribers' behaviour…" I think this statement is questionable and not really necessary. I think it's enough to say the study has "examined information in ads that may affect prescribers' behaviour" 5. I have some concerns about Table 5. First, why do all three countries have a score of 1 on the last criterion? Second, I'm wondering if it's reasonable to give different scores to countries when there are no significant difference, and to give same weight to significant and non-significant differences and large and small/uncertain differences (e.g. safety information, which is based on very few ads, especially for Australia). Third, I'm wondering about the RRR/ARR/NNT criterion: shouldn't the US be "penalised" for having many ads with RRR rather than ARR/NNT? 6. I thought the second part of the paper on "appeals and portrayals" was very interesting. However, it was not entirely clear to me what exactly this part added to the overall argument about different regulatory regimes. 7. I didn't understand the statement in parenthesis regarding the PAAB Code in the Discussion. 8. There seems to be a typo in Table 3, in the cell that reports on the frequency of ads with adverse effect info/contraindication in the US.

REVIEWER	Kenneth C. Wilbur University of California, San Diego United States of America
REVIEW RETURNED	05-Dec-2019

GENERAL COMMENTS	Review of bmjopen-2019-034993 Authors seek to quantify how prescription drug advertisements in medical journals vary between Australia, Canada and the U.S. They construct a typology of advertisement features and then use the prescription-relevant information provided in each ad to proxy for "advertisement quality." They randomly sample 15 advertisements published in family practitioner-focused journals in each country in each of two years (2014, 2015). The analysis shows that drug ads in the U.S. contain the most prescriber-relevant information, but the information provided is not always the highest quality. Authors are appropriately careful to avoid causal inferences and statements. In general I find the topic to be compelling and the analysis to be competently performed. I appreciated certain aspects of the information coding scheme. In particular, I think it is very compelling to code the methodologic quality of studies referenced and the studies' relevance to the claims. I agree with the authors that their findings should be relevant to policy. I also thought the analytical methods were appropriate and the level of significance was reasonable given the sample size. I hope the following ideas and questions may be helpful to the authors. I focus on a few big-picture issues and a few smaller details. To be clear about my own limitations, I am not a physician and therefore do not evaluate the subjective trade-offs incorporated

in the content coding scheme. Further, I am not intimately familiar with the three countries' drug advertising content regulations.

In social science journals, it is quite common to expand analyses and rewrite papers from scratch at a revision stage. I am less familiar with regular norms at journals like BMJ Open. I hope the editor will give the authors specific guidance as to how to interpret or respond to the points below.

1. Contribution

Table 1 and some discussion overviews some regulatory differences between the three countries. However, the paper does not describe specific regulations pertaining to the content of advertising, or why the difference in industry self-regulation is the most important regulatory difference between countries.

After I read the abstract, but before I read the article, I assumed that there are some differences in countries' regulations regarding what information must accompany product benefit claims in ads. For example, this webpage
https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads#risk_disclosure
says:
"Print product claim ads may make statements about a drug's benefit(s). They must present the drug's most important risks in the main part of the ad ("fair balance"). These ads generally must include every risk, but can present the less important risks in the detailed information known as the 'brief summary.'" Are the rules in Australia and Canada the same?

If the three countries differ in the information required to be included in drug ads, and if drug advertisers comply with requirements, then it is perhaps not too surprising that advertisement content differs. Perhaps it would be worthwhile to write the article in a way that anticipates this naive criticism, and helps the reader to understand the content regulatory requirements in a more thorough way.

As a specific example of this, I think the "a priori assumption" passage in section 1 would be more helpful if you explain what specific system differences lead to the hypothesis that Australia would have lower-quality ads than the US. I could imagine the differences are deeper than the aspects listed in Table 1, and relate to differences in specific content requirements between the regulatory regimes.

2. Sampling and confounds

Authors seem to have the following mental model:
Regulatory environment determines ad content (what brands say in ads).

I began with a different mental model:
Regulatory environment determines what brands advertise; how much each brand spends; and ad content (what brands say in ads).

By randomly sampling published ads, we abstract away from which brands advertise and how much they spend on ads. We focus exclusively on the claims themselves. Do the differences in ad content occur because brands adopt different advertising strategies

	in each country? Or do the differences occur because different brands advertise in each country, and therefore different types of things are said? My preferred research design would have been to determine which brands advertised the most overall; and then compare those brands' journal advertisements across the three countries. I would also be very interested to know how those brands differ in their advertisements' frequency and prominence in each country. I mention prominence because prominent advertisements typically cost more than less obtrusive ad slots. Although such a design means that the sample may be less representative of the populations of each country's drug ads, it would better reflect the most important advertisers, and would allow for a cleaner separation of advertiser from advertising content. I do not mean to invalidate the authors' design. On the contrary, I find it compelling and informative. I merely want to encourage them to consider using a different design, whether doing so may be relevant to the current study or future work. 3. Advertising "quality" In the marketing literature, the term "quality" is loaded because it is inherently subjective. You could probably construct scenarios in which two different physicians with the same goals and training might reach different judgments regarding the relative importance or desirability of various informational elements. Normally, I would encourage authors to eschew the word "quality" and directly name the construct they aim to measure, rather than using the generic label. Minor: - Page 4 mentions ROI calculations for journal advertisements. Normally advertising sellers would publicize observational studies of advertising effects in hopes of increasing naive clients' ad spending; causal effects in advertising are typically difficult to power appropriately, and experiments are rare. An additional reason to care about journal ad content is that, typically, we would expect advertising content to reflect central selling pitches made in detailing visits. Marketers believe communication efforts to be most effective when the most important elements are repeated multiple times. This is often the reason that agencies and academics emphasize "integrated marketing communications," a practice that seeks to unify the seling message across various communications channels (e.g., advertising and detailing). - I suggest you report the total number of ads published within each country/year. - Page 14 says "self-regulatory systems...yield the lowest quality ads." I don't think authors can separate the self-regulatory aspect of Australia's system from other aspects of the system, unless they first establish an absence of other relevant differences between the 3 regulatory systems. A weaker version of this statement might be advisable.

	- Page 17 was very interesting. It made me wonder why readers, regulators or physicians' societies do not hold the journals themselves responsible for the accuracy and quality of the drug ads they publish. Establishing a system that requires prescription-relevant information be communicated in drug ads could arguably directly benefit reputable drug manufacturers. If such a system ensures that drug ads are directly helpful to physician readers, then presumably the ads would receive more attention. I do not disagree with the authors' claim about well-resourced government regulation; but it may not be the only way to accomplish the goal, and it also may not be the fastest or the best way. - There are two minor typos: "were did not find" on page 13 and a p-value in table 4.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is an interesting, well-researched and well-written paper that I think ultimately should be published. However, I have a few comments and questions to the authors which I list below.

1. My main concern pertains to the key claim that observed differences in ad quality must reflect differences in the regulation of drug promotion e.g. in Abstract conclusion. It's clear that this is one possibility, but couldn't differences (also) be caused by various other regulatory, legal, cultural or health system factors that differ between countries and that cannot easily be controlled for in this study. For example, could the fact that US ads more often contain warnings/contraindications, and give more prominence to safety information, reflect industry concerns with litigation rather than FDA regulation per se. Could some differences (e.g. reference to surrogate endpoints) reflect differences in labelling rather than drug promotion oversight? And what about differences in journal ad polices? Etc.

Thank you for bringing this point to attention. We agree that this was certainly a limitation in our study. This was mentioned in our limitations section, "We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to specific national differences to each country. To the extent that our findings do reflect different regulatory regimes, they only apply to ads in family practice journals in three developed countries over the time period 2014-2015." We have incorporated the additional possible explanations for the differences mentioned by the reviewer into the Limitations section of the manuscript.

2. Related to the previous point, I think the argument about the causal link to drug advertising regulation would become more compelling if the authors present one or more putative mechanisms that could explain differences. One problem, however, that I see here is that some of the criterion that are being evaluated, although pertinent to drug prescribing, might not be considered relevant criterion to drug promotion regulators. Still, the paper's argument would be stronger if the authors could show that low quality ads either violate regulations/industry codes (suggesting weaker oversight in Australia/Canada) or that FDA regulations are more demanding (suggesting weaker rules in Australia/Canada), or both.

Thank you for your insightful comments. When reviewing the Codes for drug promotion in each country, we found that they are largely similar with respect to their general principles and by extension their specific advertising requirements. For instance, some general principles of each regulatory framework are stated below:

Australia (Code 18th edition): “The content of all promotional material provided to healthcare professionals must be current, accurate, balanced and fully supported by the Australian Approved Product Information”

Canada (PAAB Code 2013): “PAAB ensures that any information provided about a product is evidence-based and that there is a balance between claims about benefits and possible risks.”

US (https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads): “Product claim ads must present the benefits and risks of a prescription drug in a balanced fashion.”

We have incorporated the above short descriptions of the goals of the regulations into our Introduction to make the point that the overall objective of how regulations should present information about the drugs in advertisements is broadly similar.

Each country’s Code supports the provision of accurate and balanced information with respect to many of the parameters we studied (e.g. mentioning of generic name after brand name, balance between treatment benefit and harm, claims of benefit or harm supported by peer-reviewed studies, etc.). The overall goal of each regulatory body appears largely similar with respect to the message that the advertisements should convey. Therefore, advertisement differences observed among countries may also be attributed to factors such as violations in regulations.

For instance, the Codes for all countries require that advertisements depict a fair balance between benefits and side effects. Despite this, the US (75%) demonstrates this significantly more than Australia (25%) and Canada (28.6%). Despite this, our study was not designed to look for violations of the various codes. This has been added to the Limitations section.

3. Further to this point, the authors argue in the Discussion that their study show that the US government has failed to adequately control journal advertising, possibly due to limited resources, but in the Limitation section they acknowledged that the study has not considered if ads conformed to regulatory requirements.

Thank you for pointing out this inconsistency. We agree that there should be further clarification to avoid confusion as the first statement about the US government failing to adequately control journal advertising implies that we assessed if it conformed to regulatory requirements. We did not assess if ads conformed to regulatory requirements, so we have changed the first statement in the discussion to “The limitations seen in US advertisement quality might be due to a lack of resources needed to properly evaluate the volume of advertising.”

4. It is stated that this study “is the first to examine information in ads that may affect prescribers’ behaviour…” I think this statement is questionable and not really necessary. I think it’s enough to say the study has “examined information in ads that may affect prescribers’ behaviour”.

We agree that it will be better to change this statement. We have applied what you suggested.

5. I have some concerns about Table 5. First, why do all three countries have a score of 1 on the last criterion? Second, I’m wondering if it’s reasonable to give different scores to countries when there are no significant difference, and to give same weight to significant and non-significant differences and large and small/uncertain differences (e.g. safety information, which is based on very few ads, especially for Australia). Third, I’m wondering about the RRR/ARR/NNT criterion: shouldn’t the US be “penalised” for having many ads with RRR rather than ARR/NNT?

Thank you for bringing up your concerns. We are in complete agreement that it may not be reasonable to give different scores to countries when there are no significant differences. We have since adjusted our scoring system such that in the overall analysis, we only included criterion where countries significantly differed. From there, ranks were given to countries based on their medians and ranges, or their proportions. If two countries had the same median or proportion, they received the same score. We have added this explanation to the Methods section to clarify our scoring system. Additionally, we did not penalize the US for having ads with RRR rather than ARR/NNT. While it is true that data reported as ARR/NNT has been shown to lead to more conservative prescribing than RRR itself, it is unclear how prescribers are influenced by RRR versus no reporting at all. Since the US was the only country to report any ARR/NNT data as well as report quantitative data the most often, we ranked it the highest. Australia and Canada rarely provided any quantitative data. Finally, we made the appropriate changes to Table 5, but our conclusions have not changed.

6. I thought the second part of the paper on “appeals and portrayals” was very interesting. However, it was not entirely clear to me what exactly this part added to the overall argument about different regulatory regimes.

Thank you for your interest regarding this section of our paper. Appeals and portrayals are used by advertisements to market the product, and by doing so provide different impressions of the product to prescribers and have the potential to construct misleading associations between disease and the products. Given these implications, we included this in the analysis to see if appeals and portrayals, and by extension the impressions they provide to prescribers, differ between regulatory regimes. However, data on advertisement appeals and portrayals were not used in determining the overall ranking of countries because of the subjectivity involved in measuring it -- a point we now make in the Methods section.

7. I didn’t understand the statement in parenthesis regarding the PAAB Code in the Discussion.

Thank you for recognizing this inconsistency in our Discussion. It was not meant to be there, so we removed it.

8. There seems to be a typo in Table 3, in the cell that reports on the frequency of ads with adverse effect info/contraindication in the US.

Thank you for noticing this. We have resolved the typo.

Reviewer: 2

Authors seek to quantify how prescription drug advertisements in medical journals vary between Australia, Canada and the U.S. They construct a typology of advertisement features and then use the prescription-relevant information provided in each ad to proxy for “advertisement quality.” They randomly sample 15 advertisements published in family practitioner-focused journals in each country in each of two years (2014, 2015). The analysis shows that drug ads in the U.S. contain the most prescriber-relevant information, but the information provided is not always the highest quality. Authors are appropriately careful to avoid causal inferences and statements.

In general I find the topic to be compelling and the analysis to be competently performed. I appreciated certain aspects of the information coding scheme. In particular, I think it is very compelling to code the methodologic quality of studies referenced and the studies’ relevance to the claims. I agree with the authors that their findings should be relevant to policy. I also thought the

analytical methods were appropriate and the level of significance was reasonable given the sample size.

I hope the following ideas and questions may be helpful to the authors. I focus on a few big-picture issues and a few smaller details. To be clear about my own limitations, I am not a physician and therefore do not evaluate the subjective trade-offs incorporated in the content coding scheme. Further, I am not intimately familiar with the three countries' drug advertising content regulations.

In social science journals, it is quite common to expand analyses and rewrite papers from scratch at a revision stage. I am less familiar with regular norms at journals like BMJ Open. I hope the editor will give the authors specific guidance as to how to interpret or respond to the points below.

Thank you for your support, encouragement, and constructive feedback. We are happy to hear that you found our manuscript of interest. We are very appreciative of the time you have taken to improve the quality of our manuscript.

1. Contribution

Table 1 and some discussion overviews some regulatory differences between the three countries. However, the paper does not describe specific regulations pertaining to the content of advertising, or why the difference in industry self-regulation is the most important regulatory difference between countries.

After I read the abstract, but before I read the article, I assumed that there are some differences in countries' regulations regarding what information must accompany product benefit claims in ads. For example, this webpage
https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads#risk_disclosure
says:
"Print product claim ads may make statements about a drug's benefit(s). They must present the drug's most important risks in the main part of the ad ("fair balance"). These ads generally must include every risk, but can present the less important risks in the detailed information known as the 'brief summary.'" Are the rules in Australia and Canada the same?

If the three countries differ in the information required to be included in drug ads, and if drug advertisers comply with requirements, then it is perhaps not too surprising that advertisement content differs. Perhaps it would be worthwhile to write the article in a way that anticipates this naive criticism, and helps the reader to understand the content regulatory requirements in a more thorough way.

As a specific example of this, I think the "a priori assumption" passage in section 1 would be more helpful if you explain what specific system differences lead to the hypothesis that Australia would have lower-quality ads than the US. I could imagine the differences are deeper than the aspects listed in Table 1, and relate to differences in specific content requirements between the regulatory regimes.

Thank you for your insightful comments. We are in complete agreement with your thought process in that if the three regulatory frameworks differ in the information required to be included in drug ads, and if drug advertisers comply with requirements, then it is not surprising that advertisement content differs. However, upon comparing the Codes from each country, they are largely similar with respect to their general principles and by extension their specific advertising requirements. For instance, some general principles of each regulatory framework are stated below:

Australia (Code 18th edition): “The content of all promotional material provided to healthcare professionals must be current, accurate, balanced and fully supported by the Australian Approved Product Information”

Canada (PAAB Code 2013): “PAAB ensures that any information provided about a product is evidence-based and that there is a balance between claims about benefits and possible risks.”

US (https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads): “Product claim ads must present the benefits and risks of a prescription drug in a balanced fashion.”

We have incorporated the above short descriptions of the goals of the regulations into our Introduction to make the point that the overall objective of how regulations should present information about the drugs in advertisements is broadly similar.

Each country’s Code supports the provision of accurate and balanced information with respect to many of the parameters we studied (e.g. mentioning of generic name after brand name, balance between treatment benefit and harm, claims of benefit or harm supported by peer-reviewed studies, etc.). The overall goal of each regulatory body appears largely similar with respect to the message that the advertisements should convey. Therefore, advertisement differences observed between countries may also be attributed to factors such as non-adherence to the Code, and other regulatory, legal, cultural, or health system factors. This is mentioned in our Limitations section of the manuscript.

We now mention at the end of the Introduction that we draw on previous literature regarding voluntary self-regulation by industry to justify our a priori assumption that this method of regulation will prove to be the least effective in controlling journal advertising.

2. Sampling and confounds

Authors seem to have the following mental model:
Regulatory environment determines ad content (what brands say in ads).

I began with a different mental model:
Regulatory environment determines what brands advertise; how much each brand spends; and ad content (what brands say in ads).

By randomly sampling published ads, we abstract away from which brands advertise and how much they spend on ads. We focus exclusively on the claims themselves. Do the differences in ad content occur because brands adopt different advertising strategies in each country? Or do the differences occur because different brands advertise in each country, and therefore different types of things are said?

My preferred research design would have been to determine which brands advertised the most overall; and then compare those brands’ journal advertisements across the three countries. I would also be very interested to know how those brands differ in their advertisements’ frequency and prominence in each country. I mention prominence because prominent advertisements typically cost more than less obtrusive ad slots.

Although such a design means that the sample may be less representative of the populations of each country’s drug ads, it would better reflect the most important advertisers, and would allow for a cleaner separation of advertiser from advertising content.

I do not mean to invalidate the authors' design. On the contrary, I find it compelling and informative. I merely want to encourage them to consider using a different design, whether doing so may be relevant to the current study or future work.

Thank you for your comments. Although these suggestions go beyond the scope of our study design, this was very interesting to think about with regards to a future study design that would better reflect the most important advertisers. In addition, these suggestions would require access to data that could only be gathered through interviews, e.g., companies' decisions about the intensity of advertising for individual products. Other data such as prominence of advertising would require determining which products would be advertised in different journals and then counting ads in each journal. These efforts are well beyond the resources that we have.

3. Advertising "quality"

In the marketing literature, the term "quality" is loaded because it is inherently subjective. You could probably construct scenarios in which two different physicians with the same goals and training might reach different judgments regarding the relative importance or desirability of various informational elements. Normally, I would encourage authors to eschew the word "quality" and directly name the construct they aim to measure, rather than using the generic label.

We agree that the term "quality" is inherently subjective with regards to how it can be defined. Therefore, overall advertisement "quality" was defined from criteria from 1) information included in the advertisement, and 2) methodological quality of references. These criteria were pre-defined and could be measured objectively, which would remove ambiguity from our definition of "quality". The appeals and portrayals we measured were inherently subjective and therefore did not contribute to our definition of "quality". Appeals and portrayals were named for what they were.

Minor:

Page 4 mentions ROI calculations for journal advertisements. Normally advertising sellers would publicize observational studies of advertising effects in hopes of increasing naive clients' ad spending; causal effects in advertising are typically difficult to power appropriately, and experiments are rare. An additional reason to care about journal ad content is that, typically, we would expect advertising content to reflect central selling pitches made in detailing visits. Marketers believe communication efforts to be most effective when the most important elements are repeated multiple times. This is often the reason that agencies and academics emphasize "integrated marketing communications," a practice that seeks to unify the seling message across various communications channels (e.g., advertising and detailing).

I suggest you report the total number of ads published within each country/year.

Thank you for your suggestions. In line with the reviewer's suggestion in the Introduction, we point out the detailing and advertising operate in a synergistic fashion.

Although we agree that information about the total number of ads published within each country per year would help better contextualize our sample, there is no publicly available source of data on this topic.

Page 14 says "self-regulatory systems...yield the lowest quality ads." I don't think authors can separate the self-regulatory aspect of Australia's system from other aspects of the system, unless they first establish an absence of other relevant differences between the 3 regulatory systems. A weaker version of this statement might be advisable.

Thank you for pointing this out. We agree that we could not completely control for the self-regulatory aspect of Australia's system. As we previously noted, all three regulatory systems have broadly similar goals, however, we have revised a weaker version of the statement as you suggested.

Page 17 was very interesting. It made me wonder why readers, regulators or physicians' societies do not hold the journals themselves responsible for the accuracy and quality of the drug ads they publish. Establishing a system that requires prescription-relevant information be communicated in drug ads could arguably directly benefit reputable drug manufacturers. If such a system ensures that drug ads are directly helpful to physician readers, then presumably the ads would receive more attention. I do not disagree with the authors' claim about well-resourced government regulation; but it may not be the only way to accomplish the goal, and it also may not be the fastest or the best way.

Thank you for your insightful comments. We agree that even well-resourced government regulation would still have limitations. However, asking journals to regulate the quality of the ads that they run also comes with its impracticalities. The human resources available to different journals are quite different (e.g. New England Journal of Medicine compared to a US state medical journal) and the result could be very different quality of ads for the same product. Nevertheless, it remains difficult to ascertain what the fastest or best way to better the quality of drug advertisements, but well-resourced government regulations may be a step forward.

There are two minor typos: "were did not find" on page 13 and a p-value in table 4.

Thank you for pointing this out! The typo "were did not find" on page 13 has been resolved. However, we were unable to find identify the typo you mentioned in table 4.

VERSION 2 – REVIEW

REVIEWER	Shai Mulinari Lund University, Sweden
REVIEW RETURNED	11-Feb-2020

GENERAL COMMENTS	I'd like to thank the authors for responding to my comments and concerns. I only have three further comments. ' 1. Throughout the text, including abstract, there seems to be some inconsistency in how p-values are reported. Sometimes exact values are cited, sometimes not. Sometimes two decimals are used, sometimes up to four. 2. I think you don't need four decimals for the SDs on page 12. 3. I still think you are overstating the evidence of a causal link between regulatory regimes and ad quality. At the very least, I would suggest that you include a statement on limitations in the Conclusion section of the Abstract, i.e similar to "We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to other regulatory, legal, cultural, or health system factors specific to each country."

REVIEWER	Kenneth Wilbur University of California, San Diego
REVIEW RETURNED	04-Feb-2020

GENERAL COMMENTS	Authors reasonably addressed the points I raised in the previous review.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
I'd like to thank the authors for responding to my comments and concerns. I only have three further comments. '

Thank you for all your suggestions. They have been invaluable in strengthening our manuscript.

1. Throughout the text, including abstract, there seems to be some inconsistency in how p-values are reported. Sometimes exact values are cited, sometimes not. Sometimes two decimals are used, sometimes up to four.

Thank you for bringing attention to this. We have gone through our manuscript to reformat our statistical reporting as per the SAMPL guidelines endorsed by BMJ (Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines. Int J Nurs Stud. 2015;52(1):5-9.). The guidelines state:

"P values should be reported as equalities when possible and to one or two decimal places (e.g., P = 0.03 or 0.22 not as inequalities: e.g., P < 0.05). Do NOT report "NS"; give the actual P value. The smallest P value that need be reported is P < 0.001"

As such we have formatted all our p values to two decimal places and as equalities whenever possible. All p values less than 0.001 were reported as p<0.001.

2. I think you don't need four decimals for the SDs on page 12.

We have adjusted all our descriptive statistics according to the SAMPL guidelines. As such, our SDs are now reported with two decimal places.

3. I still think you are overstating the evidence of a causal link between regulatory regimes and ad quality. At the very least, I would suggest that you include a statement on limitations in the Conclusion section of the Abstract, i.e similar to "We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to other regulatory, legal, cultural, or health system factors specific to each country."

Thank you for the suggestion – we agree that it is important to avoid any potentially misleading interpretations of our data. We have added the statement in the Conclusion section of the Abstract to clarify that we could not determine whether differences in data were due to the regulatory framework or to other regulatory, legal, cultural, or health system factors specific to each country.

Specifically, we changed: "Different regulatory frameworks influence the quality of journal advertisements concerning all measured domains" to "Different regulatory systems influence journal

advertisement quality concerning all measured domains. However, differences may also be attributed to other regulatory, legal, cultural, or health system factors unique to each country."

VERSION 3 - REVIEW

REVIEWER	Shai Mulinari Lund University, Sweden
REVIEW RETURNED	16-Mar-2020

GENERAL COMMENTS	The authors have responded to all my comments. Thank you.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

The authors have responded to all my comments. Thank you.

Thank you for all your suggestions. They have been invaluable in strengthening our manuscript.