

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Pharmaceutical payments to certified oncology specialists in Japan in 2016: a retrospective observational cross-sectional analysis
AUTHORS	Ozaki, Akihiko; Saito, Hiroaki; Onoue, Yosuke; Sawano, Toyooki; Shimada, Yuki; Somekawa, Yurie; Tsuji, Aritsune; Tanimoto, Tetsuya

VERSION 1 – REVIEW

REVIEWER	Patrick McDonald Division of Neurosurgery, BC Children's Hospital Neuroethics Canada and Department of Surgery University of British Columbia, Canada
REVIEW RETURNED	24-Jan-2019

GENERAL COMMENTS	<p>The authors present their study of pharmaceutical company payments to Japanese oncologists in 2016. The article is timely and of importance given the recent scrutiny of industry payments to physicians worldwide. This appears to be the first review of such payments to Japanese oncologists in the literature. The authors are to be commended for the significant amount of work involved in obtaining the data and creating their own database of these payments. They conclude that the majority of Japanese oncologists receive funds from pharma for speaking, writing, and consulting fees.</p> <p>There are a number of issues that require clarification that I outline below:</p> <ol style="list-style-type: none">1. There are a number of grammatical and stylistic errors throughout the paper. If not already done, it would benefit from a review of the English grammar and style utilized.2. Line 60- define what is meant by "high income drug" or rephrase3. The authors received their data from the 71 companies in the JMPA- is this data provided voluntarily by the JPMA or required as part of a legislated or regulatory framework in Japan? Also, how is the accuracy of the data verified?4. Line 151 indicates that there are 9,154 members of the JSMO whereas line 231 indicates that there are 1081 eligible certified oncology specialists- please clarify this discrepancy.5. Throughout the paper, words like "exploitation" (line 86), "dubious" (line 361) and concludes that the motivation of the pharmaceutical companies in providing these payments is nefarious in nature and done only to promote the use of their high cost oncology drugs. While this is one possible explanation, I do not think this can be definitively concluded from the data provided and should perhaps be listed as a possible motivation. It may be sufficient to state that these financial relationships create a conflict
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	<p>of interest (COI) and that the COI may create biased prescribing patterns and raise concerns from the public.</p> <p>6. The data does not include money from stock ownership, ownership stakes, investment interests and payments from device manufacturers- why was this data not included in the analysis?</p> <p>7. Line 391- "Open Payments" should be changed to "Open Payments Database".</p> <p>8. The authors conclude that "It is essential to establish a robust, comprehensive and binding system for identifying and avoiding any and all potential conflicts of interest, of any nature, involving physicians or other medical professionals, both in Japan and internationally" but make no suggestions about what that system should be or what it would look like ie. Banning any and all payments to physicians, versus requirements for disclosure of such payments in a publically available manner, like the US Open Payments Database. Please clarify.</p>
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REVIEWER	David Henry Bond University, Queensland, Australia
REVIEW RETURNED	29-Jan-2019

GENERAL COMMENTS	<p>The authors have studied the financial payments made by pharmaceutical manufacturers to specialist oncologists in Japan for the FY 2016. They claim that there is little information available to the public on the extent and magnitude of payments in that country. The aims of the study were several-fold: 1) to understand and evaluate the characteristics and distributions of financial payments made by pharmaceutical companies to oncology specialists: 2) to determine if payments by companies were tied to their products; and 3) to elucidate whether Japanese oncology specialists are obliged in any way to disclose their COIs. The study was made possible by commencement of company reporting of physician payments in 2013.</p> <p>The paper is mainly descriptive although the authors have measured some associations using multivariable techniques. The study is essentially cross-sectional, but this is acceptable because the study subjects were qualified for substantial periods before the year of reporting by pharmaceutical companies and reverse causality is unlikely.</p> <p>Generally, I think the study was well done and clearly reported. I think the data are valuable in providing further insights about industry professional relationships in an important pharmaceutical market where this information has been lacking.</p> <p>My comments are relatively minor:</p> <p>1) In the Abstract the Results are reported as: "The total and mean monetary value of payments from pharmaceutical companies was ¥598,286,743 [\$5,315,718], and ¥553,457 [\$4,917] (standard deviation ¥1,264,398 [\$11,234]), respectively." This is ambiguous – I am unclear whether the authors are referring to the total and mean payments by companies or whether the mean refers to the average per capita payments to oncologists. The language needs to be clearer.</p>
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	<p>2) In the Background the authors use pejorative language – e.g. “Pharmaceutical policy-making and medical practice is riddled with opportunities for exploitation, especially given the huge amounts of money involved” I am no defender of industry pricing practices, but I think this language needs to be toned down. There is no doubt that the industry business model has shifted from blockbuster drugs used by millions to more precise targeting of smaller numbers of individuals at high per capita costs, but there are better ways of describing this.</p> <p>3) The authors write “With ageing populations, pollution, poor or excessive nutrition and the like cancer became an ever-increasing and major problem.” I think their description of cancer epidemiological trends and etiologic factors could be more comprehensive with appropriate references.</p> <p>4) In reporting the results by oncologist, the authors reports mean (with SD) median and IQR. The SD values are approximately twice the means so I think they should stick to median and IQR. In doing this they should exclude oncologists with zero payments (see below)</p> <p>5) The authors say that payments were broken into 3 groups – for speaking, writing and consulting. Are they able to report total or individual payments for these activities?</p> <p>6) In their multivariable analyses that have studied all oncologists and separately those paid Y1m or more. I think there should be three groups – those who received no payments, those who received between Y1 and Y1m and those who received more than Y1m. A comparison of the demographics and other characteristics of these three groups would be valuable</p> <p>7) In the multivariable analysis they provide incidence rate ratios. They have not performed a cohort analysis or case-control study with risk set sampling, so I am unclear how they can calculate rate ratios – would odds ratios not be more appropriate?</p> <p>8) In regard to the information on COI policies this is mentioned only briefly at the end of the Results section. This is confined to the Japanese Society of Medical Oncology and deals only with disclosure of financial ties. Does the JMSO have guidelines on how potential COI should be managed? And what about the oncologists’ home institutions – hospitals, universities and research institutes? Do they have COI disclosure/management policies?</p> <p>9) Finally, I think Table 5 should be a supplementary table.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. There are a number of grammatical and stylistic errors throughout the paper. If not already done, it would benefit from a review of the English grammar and style utilized.

Reply:

We have fixed the grammatical and stylistic errors as much as possible in this revision.

2. Line 60- define what is meant by “high income drug” or rephrase

Reply:

We have clarified this point in the revision, as follows.

(Lines 43 to 44 in the revised version),

“analyzed oncology drugs with annual sales of ¥5 billion [£33.9 million, €40.2 million, \$46.0 million] or above (hereafter high-income drugs)”

The authors received their data from the 71 companies in the JMPA- is this data provided voluntarily by the JPMA or required as part of a legislated or regulatory framework in Japan?

Reply:

Thank you. These disclosures have not been done under the Japanese registration. Instead, the Japan Pharmaceutical Manufacturers Association (JPMA) independently created the transparency guidelines, and the companies belonging to the JPMA have been required to publish their payment data under this guideline. To clarify this, we have revised the manuscript, as follows.

(From lines 151 to 154 in the revised manuscript),

“In 2011, the JPMA published transparency guidelines requiring all member companies to disclose all payments for speaking, writing and consulting made to all individuals, specifying their names and affiliations.²⁵”

Also, how is the accuracy of the data verified?

Reply:

We have addressed this point in the revised manuscript, as follows.

(From lines 471 to 478 in the revised manuscript),

“First, there could be measurement errors in the affiliations and subspecialties of the included speculates, as we speculated the accuracy of these data in the study year (2016), mainly using the affiliation websites and other data sources on the Internet. Second, there might be minor measurement errors in the payment database as well. Most of the pharmaceutical companies involved did not disclose their payment data in a uniform or readily available format. As a result, we manually entered all the payment data from a variety of formats, and, despite repeated and careful review, the database may include minor errors.”

4. Line 151 indicates that there are 9,154 members of the JSMO whereas line 231 indicates that there are 1081 eligible certified oncology specialists- please clarify this discrepancy.

Reply:

Among the 9154 members of the JSMO, 1081 are specialists certified by the JSMO. We have addressed this point in the revised manuscript.

(From Lines 170 to 177 in the revised manuscript),

“The Japan Society of Medical Oncology (JSMO), with over 9154 general members, is the one of the largest professional medical societies in the clinical oncology field in Japan. The JSMO began operating a specialty registration system for members in 2004. This required JSMO members wishing to be certified to meet specific requirements for both oncology care and academic achievement. Only after passing the requisite examination, could they become board-certified oncology specialists with renewed certification of every 5 years. We included all oncology specialists certified by the JSMO as of April 1st, 2016.”

Throughout the paper, words like “exploitation” (line 86), “dubious” (line 361) and concludes that the motivation of the pharmaceutical companies in providing these payments is nefarious in nature and done only to promote the use of their high cost oncology drugs. While this is one possible explanation, I do not think this can be definitively concluded from the data provided and should perhaps be listed as a possible motivation. It may be sufficient to state that these financial relationships create a conflict of interest (COI) and that the COI may create biased prescribing patterns and raise concerns from the public.

Reply:

We appreciate your valuable comments on our article. We have decreased the tone of the expressions, throughout the manuscript.

The data does not include money from stock ownership, ownership stakes, investment interests and payments from device manufacturers- why was this data not included in the analysis?

Reply:

We have addressed these points in the limitation section of the manuscript, as follows.

(From lines 478 to 484 in the revised manuscript),

“Third, the present research analyzed only limited payment types. Currently, Japanese pharmaceutical companies do not disclose payment data for stock interest, royalties, and costs of meals, transportation, and accommodation. As, unlike the pharmaceutical companies, the JMSO and other similar academic and learned societies in Japan, where such data may be registered, refuse to open their databases to public scrutiny, we were not able to consider these data in this study.”

7. Line 391 “Open Payments” should be changed to “Open Payments Database”.

Reply:

We have revised the expression, as follows.

(From lines 442 to 443 in the revised manuscript),

“New schemes along these lines, such as the US’s Open Payments Database, may prove successful but it is too soon to know.³⁷”

The authors conclude that “It is essential to establish a robust, comprehensive and binding system for identifying and avoiding any and all potential conflicts of interest, of any nature, involving physicians or other medical professionals, both in Japan and internationally” but make no suggestions about what that system should be or what it would look like ie. Banning any and all payments to physicians, versus requirements for disclosure of such payments in a publicly available manner, like the US Open Payments Database. Please clarify.

Reply:

We appreciate your comment. We consider that banning all payment to physicians would be not realistic, and to pursue a transparency between pharmaceutical companies and physicians would be a better choice. We have addressed this point in the revised manuscript.

(From Lines 460 to 464 in the revised version),

“While it is too early to evaluate whether similar systems, such as the US-based Open Payments Database, will be truly effective, financial transparency is a fundamental component in illustrating that there is an open, honest and ethically correct relationship between pharmaceutical companies and physicians.”

Reviewer: 2

In the Abstract the Results are reported as: “The total and mean monetary value of payments from pharmaceutical companies was ¥598,286,743 [\$5,315,718], and ¥553,457 [\$4,917] (standard deviation ¥1,264,398 [\$11,234]), respectively.” This is ambiguous – I am unclear whether the authors are referring to the total and mean payments by companies or whether the mean refers to the average per capita payments to oncologists. The language needs to be clearer.

Reply:

Thank you, but in this revision, we have erased this expression.

In the Background the authors use pejorative language – e.g. “Pharmaceutical policy-making and medical practice is riddled with opportunities for exploitation, especially given the huge amounts of money involved” I am no defender of industry pricing practices, but I think this language needs to be toned down. There is no doubt that the industry business model has shifted from blockbuster drugs used by millions to more precise targeting of smaller numbers of individuals at high per capita costs, but there are better ways of describing this.

Reply:

Thank you. We have toned down the language of the expressions, as follows.

(From lines 104 to 106 in the revised manuscript),

“For the pharmaceutical industry, medical and therapeutic practice generates substantial income, allowing it to satisfy market demand and exploit various opportunities to expand their own profits.³⁻⁵”

The authors write “With ageing populations, pollution, poor or excessive nutrition and the like cancer became an ever-increasing and major problem.” I think their description of cancer epidemiological trends and etiologic factors could be more comprehensive with appropriate references.

Reply:

We have addressed this point in the revised manuscript, as follows.

(From lines 85 to 102 in the revised manuscript),

“Cancer has been the leading cause of mortality in Japan since 1981. The government introduced its first Comprehensive 10-year Strategy for Cancer Control (1984-1993), followed by a New 10-year Strategy to Overcome Cancer (1994-2003) and a third Comprehensive 10-year Strategy for Cancer Control in 2014, aimed at boosting cancer research and provide high-quality cancer interventions and services. In 2015, an “Acceleration Plan for Cancer Control” was proposed with three key foci, “prevention”, “treatment/research” and “coexistence with cancer”, with a Basic Plan to Promote Cancer Control Programs being approved in 2017. In 2016, the year our study covered, there were 372,986 cancer deaths in Japan, with malignant neoplasms costing the nation an estimated ¥3.6

trillion [£24.4 billion, €28.9 billion, \$33.1 billion] in medical expenditure. In males, lung cancer was the leading cause of cancerous deaths (52,430) in 2016, followed by gastric cancer (29,854) and colorectal cancer (27,026), while colorectal cancer was the leading cause of cancerous death in females (23,073), followed by lung cancer (21,408) and colorectal cancer (17,405), in the same year.¹ The risk factors for cancer are diverse, including tobacco use, infection, obesity, radiation exposure, reproductive and hormonal factors, and other environmental and occupational pollutants and carcinogens.² In case of Japan, primarily with the population ageing, its cancer death is estimated to continuously increase in future.¹”

(From lines 109 to 112 in the revised manuscript),

“Following advances of drug development against infectious and chronic diseases, cancer became an ever-increasing and major problem, with 17.2 million incidents and 213.2 million cancer-associated disability-adjusted life-years (DALY) lost during 1990-2016 worldwide.⁹”

In reporting the results by oncologist, the authors reports mean (with SD) median and IQR. The SD values are approximately twice the means so I think they should stick to median and IQR. In doing this they should exclude oncologists with zero payments (see below)

Reply:

In this revision, we have quitted using the mean and standard value for the monetary value. While we included the zero values for calculating the median and IQR in the overall population, we have separately calculated these estimates for those receiving no payment in Table 3.

The authors say that payments were broken into 3 groups – for speaking, writing and consulting. Are they able to report total or individual payments for these activities?

Reply:

Thank you. We have addressed this point in the revised manuscript.

In their multivariable analyses that have studied all oncologists and separately those paid Y1m or more. I think there should be three groups – those who received no payments, those who received between Y1 and Y1m and those who received more than Y1m. A comparison of the demographics and other characteristics of these three groups would be valuable

Reply:

We appreciate your comments. To address your points, in the revised version of Table 3, we have shown the demographics of the three groups (¥1 million or more, ¥1 – 1 million, 0). Further, we separately performed the regression analyses for those receiving less than ¥1 million (Table 4).

In the multivariable analysis they provide incidence rate ratios. They have not performed a cohort analysis or case-control study with risk set sampling, so I am unclear how they can calculate rate ratios – would odds ratios not be more appropriate?

Reply:

Thank you. We apologize for an unclear expression for this. Generally, Stata expresses the output of negative binomial models as incidence rate ratio, and we used this in the previous draft. In this revision, we have expressed outputs of negative binomial models as relative monetary value, instead.

In regard to the information on COI policies this is mentioned only briefly at the end of the Results section. This is confined to the Japanese Society of Medical Oncology and deals only with disclosure of financial ties. Does the JMSO have guidelines on how potential COI should be managed? And

what about the oncologists' home institutions – hospitals, universities and research institutes? Do they have COI disclosure/ management policies?

Reply:

We apologize for an unclear expression for this matter. We have addressed this point in the revised manuscript, accordingly.

(From Lines 345 to 357 in the revised version),

“The JSMO has guideline on the COI disclosure for its members. Its members are required to disclose their COIs associated with publications and other research presentations. Further, executive board members, auditors, and other high-class members, as well as presidents and vice-presidents of conferences and committee members under the JSMO are required to disclose their COIs associated with their works and positions. These include, with respect to any for-profit organization, reporting any 1) Position as an officer or advisor, 2) Stock ownership, 3) Patent royalties or licensing fees, 4) Honoraria (e.g. lecture fees), 5) Fees paid for any writing or publication work, 6) Receipt of research funding, 7) Advisory fees or financial remuneration in exchange for testimony, 8) Acceptance of researchers from any for-profit enterprise, 9) Endowed chairs offered, and 10) Remuneration (travel, gifts, or other in-kind payments not directly related to research). However, there are no specific rules specifically referring to oncology specialists.”

Finally, I think Table 5 should be a supplementary table.

Reply:

We have changed Table 5 into Supplementary Table 3.

VERSION 2 – REVIEW

REVIEWER	Patrick McDonald University of British Columbia and BC Children's Hospital Canada
REVIEW RETURNED	19-Apr-2019

GENERAL COMMENTS	<p>The authors are to be commended for addressing a significant issue relating to industry relationships with Japanese specialist oncologists and have detailed an important issue regarding conflicts of interest in this physician population.</p> <p>The authors have addressed many of the concerns outlined in my initial review. I provide a few suggestions below:</p> <p>1. Abstract</p> <p>High income drugs- change to high revenue generating</p> <p>There should be specific COI rules covering oncologists- change to “given the frequency of industry relationships, specific COI guidelines should be developed to ensure transparency and public trust.</p> <p>2. 176- We included all oncology specialists certified by the JSMO as of April 1st, 2016. – please list how many this is</p> <p>3.</p>
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	<p>412- As we have demonstrated, there is an emphatic financial relationship between- Suggest using a different word than emphatic- significant financial relationship?</p> <p>5.</p> <p>I remain concerned that the authors conclusions regarding the motives behind payments, although a possible motivation, remains unproven and as such should be further toned down.</p> <p>6. The most significant concern I have is that there remain stylistic, grammatical and word choice issues throughout the paper that impair the flow and readability and occasionally make the manuscript difficult to follow. It would benefit from a thorough rewriting to address this.</p>
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REVIEWER	David Henry Bond University, Gold Coast, Australia
REVIEW RETURNED	24-Apr-2019

GENERAL COMMENTS	<p>I have only minor remaining comments:</p> <p>Page 6 lines 101-103 "In case of Japan, primarily with the population ageing, its cancer death is estimated to continuously increase in future.1" This could perhaps be replaced by "In Japan, principally because of its ageing population, cancer rates are estimated to continue to rise."</p> <p>Page 12 lines 206-210 "We speculated the cancer specialties (respirology, gastroenterology, hematology, breast, etc.) of all oncologists who received total payment of ¥1 million [£6.8 thousand, €8.0 thousand, \$9.2 thousand] or above from the included pharmaceutical companies, using data from institutional websites and other sources as well." I regret I do not know what this sentence means.</p> <p>Page 20 lines 347-350 "Further, executive board members, auditors, and other high-class members, as well as presidents and vice-presidents of conferences and committee members under the JSMO are required to disclose their COIs associated with their works and positions." This could be slightly reworded "Further, executive board members, auditors, and other highly ranked members, as well as presidents and vice-presidents of conferences and JSMO committee members, are required to disclose COIs associated with their works and positions"</p> <p>I think the Concluding Remarks should follow the section on Limitations</p> <p>In Table 4 top line it might be helpful to indicate that the relative monetary value is expressed as per year following board certification.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

1. Abstract

High income drugs- change to high revenue generating

Reply:

We appreciate your comments. We have revised the phrasing followingly.

(From lines 45 to 46 in the revised manuscript),
“high revenue generating drugs”

There should be specific COI rules covering oncologists- change to “given the frequency of industry relationships, specific COI guidelines should be developed to ensure transparency and public trust.

Reply:

We appreciate your comments. We have revised the phrasing followingly.

(From lines 60 to 62 in the revised manuscript),
“Given the frequency and amounts of money involved in such linkages, it would be beneficial for specific COI regulations to be developed and policed for oncologists.”

2. 176- We included all oncology specialists certified by the JSMO as of April 1st, 2016. – please list how many this is

Reply:

We appreciate your comments. We have revised the phrasing followingly.

(From lines 204 to 205 in the revised manuscript),
“All 1,081 oncology specialists certified by the JSMO as of April 1st, 2016, were included in this study.”

3. 412- As we have demonstrated, there is an emphatic financial relationship between- Suggest using a different word than emphatic- significant financial relationship?

Reply:

We appreciate your comments. We have slightly revised the phrasing followingly.

(From lines 465 to 466 in the revised manuscript),
“As we have demonstrated, there are extensive financial relationships between pharmaceutical companies and oncologists in Japan.”

5. I remain concerned that the authors conclusions regarding the motives behind payments, although a possible motivation, remains unproven and as such should be further toned down.

Reply:

Thank you for your advice. Given that the ultimate goal of the Pharma is obviously a pursuit of profits, it is reasonable to consider that the payments to physicians were used for the drug promotions. Indeed, a majority of the authors are local healthcare professionals in Japan, and we understand this from our experiences. Still, we have slightly toned down the conclusions of the article, following your suggestions, as follows.

(From lines 527 to 547 in the revised manuscript),
“Concluding remarks

Japanese certified oncologists receive financial payments directly from pharmaceutical companies, usually from companies active in the specialist field of the physician in question. In today's prevailing climate of Fake News, inaccurate scientific data, Vaccine Hesitancy, and suspicion about many

financial dealings involving Pharma, this raises several queries with regard to ethical, medical, and legal issues. The value and specialty targets of the payments varied substantially, which also raises yet more questions as to why. We believe that the lessons learned from our analyses should be shared among the global medical community to help put in place safeguards to prevent any form of inducements from the pharmaceutical industry and to help protect physicians from outside influences. It is essential to establish a robust, comprehensive and legally-binding system for identifying and avoiding any and all potential COIs, of any nature, involving physicians or other medical professionals, both in Japan and internationally. While it is too early to evaluate whether similar systems, such as the US-based Open Payments Database, will be truly effective, financial transparency is a fundamental component in illustrating that there is an open, honest and ethically correct relationship between pharmaceutical companies and physicians. A more comprehensive study is planned, to include all Japanese oncologists, to try and confirm our findings and to help identify the best way forward to ensure that COIs are minimized and so that physicians and pharmaceutical companies can work harmoniously and synergistically to provide Japan with the best cancer prophylaxis, treatment and cures possible.”

6. The most significant concern I have is that there remain stylistic, grammatical and word choice issues throughout the paper that impair the flow and readability and occasionally make the manuscript difficult to follow. It would benefit from a thorough rewriting to address this.

Reply:

We appreciate your valuable comments. We have reviewed and revised the styles, grammar and word choices throughout this work.

Reviewer: 2

Page 6 lines 101-103

"In case of Japan, primarily with the population ageing, its cancer death is estimated to continuously increase in future.¹"

This could perhaps be replaced by “In Japan, principally because of its ageing population, cancer rates are estimated to continue to rise.”

Reply:

We appreciate your advice and have revised the phrasing accordingly.

(From lines 131 to 132 in the revised manuscript),

“In Japan, principally because of its ageing population, cancer rates are forecast to continue to rise for the foreseeable future.³”

Page 12 lines 206-210

"We speculated the cancer specialties (respirology, gastroenterology, hematology, breast, etc.) of all oncologists who received total payment of ¥1 million [£6.8 thousand, €8.0 thousand, \$9.2 thousand] or above from the included pharmaceutical companies, using data from institutional websites and other sources as well."

I regret I do not know what this sentence means.

(From lines 237 to 239 in the revised manuscript),

“We further estimated the primary cancer specialty (respirology, gastroenterology, hematology, breast, etc.) of all oncologists included in the study.”

Page 20 lines 347-350

"Further, executive board members, auditors, and other high-class members, as well as presidents and vice-presidents of conferences and committee members under the JSMO are required to disclose their COIs associated with their works and positions."

This could be slightly reworded “Further, executive board members, auditors, and other highly ranked members, as well as presidents and vice-presidents of conferences and JSMO committee members, are required to disclose COIs associated with their works and positions”

Reply:

We appreciate your advice, but the high-class members referred to in this sentence all belonged to the JSMO. Thus, we believe that the original sentence reflected the intended meaning more than the one you kindly suggested.

I think the Concluding Remarks should follow the section on Limitations.

Reply:

We respect your advice and have changed the order of the Concluding Remarks and Limitations.

In Table 4 top line it might be helpful to indicate that the relative monetary value is expressed as per year following board certification.

Reply:

We appreciate your comments. We have revised Table 4 following your instructions.