PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Conflict of interest among Italian medical oncologists. A national survey
AUTHORS	DeCensi, Andrea; Numico, Gianmauro; Ballatori, Enzo; Artioli, Fabrizio; Clerico, Mario; Fioretto, Luisa; Livellara, Virginia; Ruggeri, Benedetta; Tomirotti, Maurizio; Verusio, Claudio; Roila, Fausto

VERSION 1 – REVIEW

REVIEWER	Joel Lexchin York University Canada
REVIEW RETURNED	19-Dec-2017

GENERAL COMMENTS	This study uses a questionnaire to look at COI amongst Italian oncologists. 1. The English is awkward in some places and the manuscript should be thoroughly copy edited by someone whose first language is English. 2. Was ethical approval sought for this study? If not why? 3. Page 3, line 7: It is not clear what the authors mean by “more careful policy”. 4. Page 4, lines 15-17 (and page 14, lines 14-16): The fourth bullet point says that there was a non-random selection of respondents so it is hard to see why the authors are claiming that the results are generalizable. 5. Page 4, lines 21-22 (and page 14, line 9): The authors should delete “an unprecedented opportunity for transparency.” It is also possible that anonymity made respondents comfortable with not giving out full information. 6. Page 5, line 15: There is a difference between COI due to financial gain and career advancement. The former is under voluntary control whereas the latter is generally part of one’s personality and therefore very difficult to change. 7. Page 5, line 29: Why is collaboration between clinicians and industry essential for advancement? This would imply that every clinician who has advanced in her or his field has collaborated with industry. Is that really true? 8. Page 5, line 31: It is easy to see the negative consequences of a COI, i.e., that the existence of the COI might lead to disregarding the clinician’s primary obligation. What positive consequences are the authors referring to? 9. Page 5, line 33: Managing COI is not the only option. Another is avoiding COI situations in the first place. 10. Page 5, line 53: Reference 15 is now over 15 years old and may no longer be relevant and should be deleted.

	11. Page 6, lines 17-19: PPSA may increase patients' knowledge about the relationships their doctors have with industry but how will it lead to trustful patient physician relationships? 12. Page 6, lines 46-50: How were oncologists in research institutions and university hospitals included in the survey? 13. Page 6, lines 52-54: Are younger oncologists not members of CIPOMO? 14. Page 7, line 3: How were the questions in questionnaire chosen? Although Figure 1 gives the questions some of them are cut off. The full questionnaire should be provided. 15. Page 8, line 3: What was the rational for looking at geographic area of practice? 16. Page 8, line 29: What does the word "tenured" mean in this context? 17. Page 8, lines 33-35: Table 1 should have details about the demographics of all Italian oncologists so that readers can see how the respondent group compared to the entire population. 18. Page 10, Discussion: The results of this survey should be put into the context of international research on this topic - e.g.: Rochon et al. Trials 2011;12:9; Rasmussen et al. Journal of the Royal Society of Medicine 2015;108(3):101-107; Campbell et al. NEJM 2007;356:1742-50; Henry et al. Medical Journal of Australia 2005;182:557-60. 19. Page 11, lines 16-18: One-quarter of the physicians receiving payments were women but what percent were women of the overall sample? 20. Page 13, lines 44-53: How does the sentence on the R&D costs of new cancer drugs relate to the topic of COI? 21. Page 14, lines 30-40: The recommendations on lines 30-41 are very vague. I would like to see more specific policy recommendations put forward.

REVIEWER	David Menkes University of Auckland, New Zealand
REVIEW RETURNED	04-Jan-2018

GENERAL COMMENTS	This study addresses an important topic, and the authors are to be commended for having planned and executed it on their own, apparently without external support and without pressure to do so. It's also worth noting that the survey does ask important questions of the respondents, and the results do provide the basis for discussion and debate about how to appropriately manage conflicts of interest in the setting of Italian oncology. However, the manuscript does have a number of problems: 1. the use of English needs to be improved. Apart from minor and understandable grammatical errors, throughout the manuscript there are a number of instances of idiosyncratic language use that compromise clarity and meaning. For example, what are "medical stakeholders"? An "escalating prize system"? "Financial toxicity to patients"? 2. The survey methodology needs to be clarified. Were the email invitations to participate sent only to the 184 hospital oncology chiefs? How many of them responded (Table 1 suggests that 98 may have done so)? How many would have promulgated the survey to their staff? How then were other oncologists (non-staff members) contacted and invited? 3. The paper appears to lack potentially important comparison data. Have there been studies of oncologists in other countries? If so, these need to be referenced and their results considered. If not, this needs to be made explicit. Likewise, have similar questions been

	asked of non-oncologists in Italy? Elsewhere? (I was unconvinced by the authors' statement toward the end that "…little is known about the medical perception and experience of the problem, particularly in Europe"). Finally, the paper usefully mentions the importance of patient attitudes, but have patient surveys included similar questions? With what results? 4. The Discussion requires development and focused take-home messages. While the findings aren't terribly surprising, some are disturbing, such as the proportions of respondents that don't see anything wrong with allowing drug companies to select speakers for CME, or to fund attendance at drug company events, or those that rely on pharmaceutical representatives for their CME. More detailed results and discussion would be useful regarding these points and also the determinants of attitudes regarding disclosure of COI. The results overall seem to indicate a need for education about, inter alia, the effect of sponsored education on attitudes and on prescribing behaviour -- this could be developed in an expanded Discussion. It likewise seems that many respondents are unaware of the extent to which industry sponsorship affects clinical trial results. These points could be emphasised in the "what this study adds" section.

VERSION 1 – AUTHOR RESPONSE

AU: We thank the Editor and the reviewers for their constructive comments which have certainly improved our manuscript. Below please find our point by point reply to the reviewers' comments.
1) Please remove the 'what is already known' and 'what this study adds' sections (these are not journal requirements).
2) Please elaborate on why ethics approval was not required for this study.
3) Along with your revised manuscript, please provide a completed copy of the STROBE checklist (http://www.strobe-statement.org/).
4) Please thoroughly copy-edit the paper. We recommend consulting a native English speaker/ professional copy-editing service.

AUTHORS:
1) We removed the what is already known' and 'what this study adds' sections.
2) The questionnaire was authored by three members of CIPOMO, a private association of medical oncologists, and reviewed by the eight members of the CIPOMO board of directors. We felt ethics approval was not required because the research survey was morally acceptable and could not risk harming the study participants, a group of Italian medical Oncologists. A sentence on this issue has been added on page 7. However, we are ready to submit the study to an Ethics Committee before publication if this is deemed necessary by the Journal.
3) A complete STROBE checklist copy is provided.
4) We consulted a professional native English speaker to review our manuscript.

Reviewer 1.
This study uses a questionnaire to look at COI amongst Italian oncologists.
1. The English is awkward in some places and the manuscript should be thoroughly copy edited by someone whose first language is English.
AU: We consulted a professional native English speaker to review our manuscript.

2. Was ethical approval sought for this study? If not why?
AU: The questionnaire was authored by three members of CIPOMO, a private association of medical oncologists, and reviewed by the eight members of the CIPOMO board of directors. We felt ethics

approval was not required in this case because the research survey was morally acceptable and could not risk harming the study participants, a group of Italian medical oncologists. Moreover, Italian legislation does not require Ethics Committee approval for research not involving patients. A sentence on this issue has been added on page 7.

3. Page 3, line 7: It is not clear what the authors mean by “more careful policy”.
AU: We changed 'careful' with 'rigorous policy' and 'discussed' with 'implemented' in the abstract conclusions.

4. Page 4, lines 15-17 (and page 14, lines 14-16): The fourth bullet point says that there was a non-random selection of respondents so it is hard to see why the authors are claiming that the results are generalizable.
AU: We changed 'generalizable' with 'well founded' in the bullet and rephrased the sentence on page 14 to acknowledge these limitations.

5. Page 4, lines 21-22 (and page 14, line 9): The authors should delete “an unprecedented opportunity for transparency.” It is also possible that anonymity made respondents comfortable with not giving out full information.
AU: we deleted “an unprecedented opportunity for transparency” in both sentences.

6. Page 5, line 15: There is a difference between COI due to financial gain and career advancement. The former is under voluntary control whereas the latter is generally part of one’s personality and therefore very difficult to change.
AU: We are uncertain about the point made by the reviewer here. Financial gain and career advancement are intimately linked in our Italian system and are both part of one's personality.

7. Page 5, line 29: Why is collaboration between clinicians and industry essential for advancement? This would imply that every clinician who has advanced in her or his field has collaborated with industry. Is that really true?
AU: Industry, by selecting centers for their clinical trials, promoting authorships of their studies and organizing participation in meetings, boards and public events, is deeply linked to career advancement. However, we changed 'are essential' to 'may contribute'.

8. Page 5, line 31: It is easy to see the negative consequences of a COI, i.e., that the existence of the COI might lead to disregarding the clinician’s primary obligation. What positive consequences are the authors referring to?
AU: We deleted 'positive' consequences.

9. Page 5, line 33: Managing COI is not the only option. Another is avoiding COI situations in the first place.
AU: We agree with the reviewer, but in the real world of medical oncology managing COI is the most realistic response.

10. Page 5, line 53: Reference 15 is now over 15 years old and may no longer be relevant and should be deleted.
AU: We replaced ref 15 with a more recent one on this issue.

11. Page 6, lines 17-19: PPSA may increase patients’ knowledge about the relationships their doctors have with industry but how will it lead to trustful patient physician relationships?
AU: There is evidence that this is the case as shown in ref. 31 (Wen, BMJ). However, we deleted 'trustful patient physician relationships'.

12. Page 6, lines 46-50: How were oncologists in research institutions and university hospitals included in the survey?
AU: Through word of mouth. We added a brief sentence in this regard.

13. Page 6, lines 52-54: Are younger oncologists not members of CIPOMO?
AU: Yes, only chiefs of staff are members of CIPOMO but we invited our collaborators to participate as well.

14. Page 7, line 3: How were the questions in questionnaire chosen? Although Figure 1 gives the questions some of them are cut off. The full questionnaire should be provided.
AU: These were chosen by three of us (ADC, GN, FR) based on outstanding issues in the medical community and approved by the Board of Directors, as described on page 7. We added a note on this and replaced figure 1 with a new figure showing the full questions .

15. Page 8, line 3: What was the rational for looking at geographic area of practice?
AU: Italy is typically divided in these three areas by the National Institute of Statistics based on historical and socio-economic reasons.

16. Page 8, line 29: What does the word “tenured” mean in this context?
AU: having a permanent position in his/her Institution.

17. Page 8, lines 33-35: Table 1 should have details about the demographics of all Italian oncologists so that readers can see how the respondent group compared to the entire population.

AU: We are unable to provide this comparison since a detailed report of individual characteristics of all Italian oncologists is not available. In the text we acknowledge that our sample may not be representative of all medical oncologists. However, the features of the sample suggest that the results of the survey are in line with the Italian oncologist’s opinions.

18. Page 10, Discussion: The results of this survey should be put into the context of international research on this topic - e.g.: Rochon et al. Trials 2011;12:9; Rasmussen et al. Journal of the Royal Society of Medicine 2015;108(3):101-107; Campbell et al. NEJM 2007;356:1742-50; Henry et al. Medical Journal of Australia 2005;182:557-60.
AU: We added a comment to put our data in context quoting a number of studies including Campbell et al and Rasmussen et al.

19. Page 11, lines 16-18: One-quarter of the physicians receiving payments were women but what percent were women of the overall sample?
AU: 46.7% as shown in table 1.

20. Page 13, lines 44-53: How does the sentence on the R&D costs of new cancer drugs relate to the topic of COI?
AU: It is related to the increase in drug prices due to expensive marketing and promotional activities, which include paying doctors for a variety of activities, as we mentioned in the introduction. We added a note on page 14 to clarify this issue.

21. Page 14, lines 30-40: The recommendations on lines 30-41 are very vague. I would like to see more specific policy recommendations put forward.
AU: We have shortened the paragraph to become less vague and added a few recommendations which are part of a COI policy document currently under preparation by CIPOMO.

Reviewer: 2
Reviewer Name: David Menkes
Institution and Country: University of Auckland, New Zealand
Competing Interests: We have recently completed and published a study on conflict of interest disclosures (https://link.springer.com/article/10.1007/s11606-017-4225-5).
My co-author in this study, Dr Alan Blum, University of Alabama, contributed to this review.

This study addresses an important topic, and the authors are to be commended for having planned and executed it on their own, apparently without external support and without pressure to do so. It's also worth noting that the survey does ask important questions of the respondents, and the results do provide the basis for discussion and debate about how to appropriately manage conflicts of interest in the setting of Italian oncology.
AU: we thank the reviewers for their praise.

However, the manuscript does have a number of problems:
1. the use of English needs to be improved. Apart from minor and understandable grammatical errors, throughout the manuscript there are a number of instances of idiosyncratic language use that compromise clarity and meaning. For example, what are "medical stakeholders"? An "escalating prize system"? "Financial toxicity to patients"?
AU: We consulted a professional native English speaker to review our manuscript. We changed 'medical stakeholders' to 'medical doctors' or 'medical oncologists' depending on the context and 'escalating prize system' to 'price increase strategy'. Financial toxicity is a term now commonly used in medical oncology as in Zafar et al (ref 19) to indicate the financial distress related to the cost of cancer treatments.

2. The survey methodology needs to be clarified. Were the email invitations to participate sent only to the 184 hospital oncology chiefs? How many of them responded (Table 1 suggests that 98 may have done so)? How many would have promulgated the survey to their staff? How then were other oncologists (non-staff members) contacted and invited?
AU: We used a passive approach to avoid intrusive claims given the sensitivity of the topic, so the denominators are unknown. The survey was posted in the CIPOMO web site for 6 weeks and two reminder emails were sent to the regional delegates of CIPOMO to advertise the survey and to involve collaborators. Questionnaires were not sent directly to CIPOMO members. This information was added in the method section.
3. The paper appears to lack potentially important comparison data. Have there been studies of oncologists in other countries? If so, these need to be referenced and their results considered. If not, this needs to be made explicit. Likewise, have similar questions been asked of non-oncologists in Italy? Elsewhere? (I was unconvinced by the authors' statement toward the end that "…little is known about the medical perception and experience of the problem, particularly in Europe"). Finally, the paper usefully mentions the importance of patient attitudes, but have patient surveys included similar questions? With what results?
AU: We are unaware of comparison data in other countries. Specifically, we were unable to find surveys on COI prompted by the medical community itself, either in oncology or other disciplines. This was mentioned on page 14. The only available data on COI pertain to the findings of PPSA which are limited to direct payments to medical oncologists in the US, who are more likely to receive a general payment and to hold ownership interest compared with non-oncologists (page 11). Patient surveys have been conducted in other countries and show a significant level of concern regarding physician-industry relationships. These works are quoted in the manuscript (refs 8-10,31,35). We also quoted the study by Menkes and Blum in the discussion on page 13 since it was relevant to our discussion.
4. The Discussion requires development and focused take-home messages. While the findings aren't terribly surprising, some are disturbing, such as the proportions of respondents that don't see anything wrong with allowing drug companies to select speakers for CME, or to fund attendance at

drug company events, or those that rely on pharmaceutical representatives for their CME. More detailed results and discussion would be useful regarding these points and also the determinants of attitudes regarding disclosure of COI. The results overall seem to indicate a need for education about, inter alia, the effect of sponsored education on attitudes and on prescribing behaviour -- this could be developed in an expanded Discussion. It likewise seems that many respondents are unaware of the extent to which industry sponsorship affects clinical trial results. These points could be emphasised in the "what this study adds" section.
AU: We felt the considerations made by the reviewers were very interesting and added them to the discussion on page 15. Furthermore, we have shortened the last paragraph to become less vague and added a few recommendations which are part of a COI policy document currently under preparation by CIPOMO.

VERSION 2 – REVIEW

REVIEWER	Joel Lexchin York University Canada
REVIEW RETURNED	02-Mar-2018

GENERAL COMMENTS	The authors have answered my initial concerns but there are a few remaining minor issues that need to be resolved. In addition, I also note that the English in this manuscript is still quite awkward in many places. Page 6, line 23: What "field" are the authors referring to? Page 7, line 39 (and elsewhere in the manuscript): It should be "continuing" not "continuous". Page 8, lines 13-15: Please be specific about the tests used rather than using "usual descriptive statistics". Page 9, line 11: Do the authors mean 319 oncology units in Italy? Page 15, line 22: What do the authors mean by "indirect"?

VERSION 2 – AUTHOR RESPONSE

The authors have answered my initial concerns but there are a few remaining minor issues that need to be resolved. In addition, I also note that the English in this manuscript is still quite awkward in many places.

AU: An English mothertongue review has been done twice. We are unable to do any better.

Page 6, line 23: What "field" are the authors referring to?

AU: "field of COI" has been added.

Page 7, line 39 (and elsewhere in the manuscript): It should be "continuing" not "continuous".

AU: we changed continuous to continuing in the text and table 4.

Page 8, lines 13-15: Please be specific about the tests used rather than using "usual descriptive statistics".

AU: we added “number and percentage” in parentheses

Page 9, line 11: Do the authors mean 319 oncology units in Italy?

AU: yes we added Units in the text.

Page 15, line 22: What do the authors mean by "indirect"?

AU: we deleted indirect and added “employee’s instituton”

VERSION 3 – REVIEW

REVIEWER	Joel Lexchin York University, Canada
REVIEW RETURNED	04-Apr-2018

GENERAL COMMENTS	The authors have satisfied my remaining concerns about the contents of the manuscript but the English remains to be improved.