PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Financial conflicts of interest of clinicians making submissions to the panCanadian Oncology Drug Review: a descriptive study
AUTHORS	Lexchin, Joel

VERSION 1 - REVIEW

REVIEWER	Cole Wayant Oklahoma State University Center for Health Sciences
REVIEW RETURNED	17-Apr-2019

GENERAL COMMENTS	Editors of BMJ Open and Dr. Lexchin: Thank you for the opportunity to review this manuscript that reports an investigation of FCOIs among authors submitting public-funding requests to the panCanadian Oncology Drug Review and how these FCOIs interplay with public-funding recommendations by pCODR. I believe this paper hits on a timely topic, given the literature on FCOIs in cancer medicine and regulatory capture at national drug agencies. Additionally, any investigation of potential bias in a national drug agency that may affect government sponsorship of oncology drugs is important given the high cost and diminutive efficacy often shown in oncology drug trials. I think the key item from my review is to determine, to the furthest extent possible, whether forces other than FCOI were in play to influence the pCODR recommendations. I have left my specific comments below. Sincerely, Cole Wayant Oklahoma State University Center for Health Sciences _____ 1. I think readers would benefit from examples of what is mean by “agreed [with funding decision]”, “agreed in part”, and “disagreed”. Specifically, it is not intuitive (at least to me) what “agreed in part” means. 2. Do you have data on the total number of individual clinicians that provided input? I am curious to know if there are key, heavily conflicted people who frequent these meetings to lobby for drug funding. 3. Related to Item 3, this entire paper reminds me of a study by Gyawali, et al in JAMA Oncology (PMID: 29522146), and a related paper by Egilman, et al (PMID: 17420438), that discuss regulatory capture. I think including a discussion of regulatory capture would strengthen this paper because it seems like that is what is happening. Table 4 highlights this – when a “fund”

	recommendation is rendered, clinicians agree. When a “do not fund” decision is rendered, clinicians disagree. It could be that clinicians are unbiased and the pCODR’s recommendations are evidence based, but more than likely the physicians who submit recommendations are biased toward the new drug. You rightly discuss that this could be because of non-FCOI reasons, but it is hard to avoid the number of FCOIs present in light of Table 4. That the government is paying for these drugs raises the stakes of these findings compared to the USFDA. 4. Would you be able to elaborate on the 1 case where the pCODR changed its recommendation from “no” to “yes – fund”? Was new evidence gathered? Did anything change in the data, or is this example the poster child of regulatory capture (refer to paragraph 1 of Egilman et al to see what I mean)? 5. I see that there are 37 preliminary recommendations and 46 final recommendations. How many final recommendations were “do not funded”? If 1/3 of the recommendations are not funded, I would be curious about a subgroup analyses between clinicians who gave input for “fund” and “do not fund” recommendations, if that is possible. a. I ask because if you find that there is a greater proportion of FCOI at “funded” drug meetings, it can help identify the effect of FCOI on the panel recommendations. 6. Are pCODR expert panelists allowed to have FCOI? 7. Do you have any policy recommendations that you would make for these pCODR meetings? For example, should it be required that the number of physicians who have FCOI be limited to 50% of speakers, since the discussion point you make shows that 46% of physicians were paid by industry in Canada. 8. Please include the start date of your sample in the Methods. I only see it in the abstract. 9. [Minor] The conclusion section of the abstract, you spelled conflicts “onflicts”.

REVIEWER	Nathaniel Robbins Dartmouth Geisel School of Medicine
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	Professor Lexchin is addressing a vitally important topic - that of financial COI between oncologists, Industry, and regulatory agencies. This a study that is narrow in scope, identifying disclosed COI amongst neurologists submitting to the pCODR. There are several places where the writing could clearer, and several places where the detail is insufficient. I will address those individually as follows: Structured Summary: Objectives: a slight introduction to the pCODR would be appropriate here to give the reader some context: "...make submission to the Canadian oncologic drug agency responsible for determining whether certain drugs should be publicly funded - the pCODR" for example. The objective is otherwise not clear unless you read a lot of the paper. Outcomes: I would change the study period to the objective section and recommend demarcating the outcomes somehow to improve clarity:

	"The primary outcome is the number and nature of FCOI between oncologists and drug companies. Secondary outcomes include ..." As written is is confusing and hard to read. Results: line 47. Would end sentence afer pCODR and start Clinicians. Line 48 - unclear who the "They" is (pCODR or clinicians). Would change to "physicians" or somehow link to prior sentences. Also, as will be addressed below, I am not clear what "naming a company" means, if not declaring a FCOI or stock ownership. This needs to be flushed out better in the methods, and probably also here in the summary. "Naming" and "Declared" are not immediately self-evident terms. Line 51/52 (And elsewhere) : might be clear with active voice : "Clinicians commented on 37 preliminary recommendations." Lines55. Should expand on what the p-value refers to. : "...with that recommendation. Clinicians were statistically more likely to disagree when the drug-funding indication was not approved, $p<0.0001$ Fisher Exact" Article Summary The first three bullet point in the strengths and limitations are descriptive of the study and not strengths or weaknesses. The second two are weaknesses. The strength is this is the first study of its kind Weakness will be detailed below Introduction: Would state upfront (line 104) whether this input is solicited or unsolicited (it is voluntary and unsolicited, as you explain later) Line 118 (and elsewhere throughout the manuscript), you should stick with FCOI or spell it out but be consistent In the Introduction there needs to be a more thorough review of why this is important. There is a big literature on how FCOI amongst physicians biases and clinical practice, research, research dissemination, education. The author is well aware of this literature and has published several important papers on the topic. Readers who are not familiar with FCOI need a more thorough background briefly reviewing why this is an important paper. Otherwise it appears quite esoteric. Methods It would be nice to have a background of how many reports were issues that did not receive submissions from a clinician. This contextualizes how frequently clinical submissions play a role in the agency's decisions. I am not clear why reconsiderations and funding for a differenr drug-indication are included. Do some physicians submit to both the initial consideration and the reconsideration? To the multiple drug-indications for the same drug? If so (and presumably the answer is yes), you need to address the methodological issue of double counting, which overestimates the relationships. You might think about presenting the data both ways if possible.

	Line 137 and 138 is confusing due to punctuation - there should be parentheses aroudn the (...e.g...consideration) Again, I am confused in the Methods - how do companies get "named" if they are not part of a FCOI. This needs to be expanded. One issue not addressed (which is a weakness of the methods that limits external validity) is that the FCOI are only self-reported. There should be a discussion of literature demonstrating that clinicians consistently underreport COI voluntarily. Another weakness that the author mentions but does not discuss at length is the fact that we cannot tell if these FCOI are relevant or not. There should be a more detailed discussion of the problem with not listing amounts. Small meal payments of $10 are diffferent than $100k consulting fees or stock options. Table 3 - again problematic because we do not know if there is double counting It would be useful to know if the physicians who agreed with the recommendation tended to have COI with that company, and compare that with physicians who disagreed with the recommendations. Were any declared COI with companies that made competing drugs? This gets at the issue of whether the FCOI are relevant or not even if you do not have access to the dollar mounts. Discussion: There has to be a discussion of the fact that the populations of submitting clinicians is self-selected and does not reflect the population of physicians as a whole. Clinicians with COI are more likely to submit. This explains the lower number (line 242) but is not addressed. Similarly, FDA advisory committees are picked randomly, rather than advisors self-selecting. Line 251 - 256 : this part (and the rest of the discussion) would benefit from some more depth. for example, a suggestion of how things could be improved. Maybe Canada needs a mandatory reporting system for payments to physicians like the OP database to address the omissions. In general I found the discussion, like the introduction, to be a little cursory. To stress the importance of this paper the author should expand these sections discussed above Limitations Conclusion The sentence from line 320 to 323 is a limitation, not a conclusion This section should probably also point out that there is too little information available publicly to assess 1) whether COI disclosures are accurate 2) whether submitting clinicians COI impact the decisions. Also the volluntary nature of the submissions leads to skewed commentary, so perhaps a panel of experts (with those with COI excluded) would be more balanced.

REVIEWER	Karla Bernardi University of Texas Health and Science Center at Houston
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	Thank you for the opportunity to review your manuscript on financial conflict of interest of clinicians making submission to the panCanadian Oncology Drug Review: a descriptive study. This study focuses on a very important issue in medical research which is the influences of financial conflict of interest in research and in approval of new medications and technology. Questions for the authors: 1. In the abstract is it not clear what is the primary outcome and which ones are secondary outcomes. Is this supposed to be a combined primary outcome? Please specify what is the primary outcome of the paper. 2. In the abstract, in the conclusion section, there is a C missing for conflict. 3. methods: were all reports for the study period that met the inclusion criteria included? 4. methods: was there a way to verify if clinicians were disclosing all their COI? 5. methods: please clarify if this is a voluntary service for clinicians to submit responses and recommendations, are they invited, or assigned these drug submissions? 6. Statistics: how did you determine that these were enough reports to find a difference? Was there a power analysis performed? Was the an expected difference? 7. I want to point out that the majority of these drug submissions were approved or approved with some changes, and over 50% of members in the committee had a FCOI. There is a possibility that such a high approval rate is influenced by the presence of individuals with COI. There are studies in medical research which show that any COI will influence the study outcomes, there is a high likelihood that this is the case here as well. 8. For table 4, I think it would be helpful if you had the information of a subgroup analysis of how many clinicians with COI within a group agreed, or agreed in part, or disagree with the decision from the pCODR. Maybe if there is a difference if over 50% of the group had a COI versus other groups with less than 50% COI

VERSION 1 – AUTHOR RESPONSE

Comment	Reply	Line number (revised version)
Reviewer 1		
I think readers would benefit from examples of what is mean by “agreed [with funding decision]”, “agreed in part”, and “disagreed”. Specifically, it is not intuitive (at least to me) what “agreed in part” means.	A definition has been provided for “agreed in part”.	165-167
Do you have data on the total number of individual clinicians that provided input? I am curious to know if there are key, heavily conflicted people who frequent these meetings to lobby for drug funding.	This information is already provided in Table 3.	
Related to Item 3, this entire paper reminds me of a study by Gyawali, et al in JAMA Oncology (PMID: 29522146), and a related paper by Egilman, et al (PMID: 17420438), that discuss regulatory capture. I think including a discussion of regulatory capture would strengthen this paper because it seems like that is what is happening. Table 4 highlights this – when a “fund” recommendation is rendered, clinicians agree. When a “do not fund” decision is rendered, clinicians disagree. It could be that clinicians are unbiased and the pCODR’s recommendations are evidence based, but more than likely the physicians who submit recommendations are biased toward the new drug. You rightly discuss that this could be because of non-FCOI reasons, but it is hard to avoid the number of FCOIs present in light of Table 4. That the government is paying for these drugs raises the stakes of these findings compared to the USFDA.	I thank the reviewer for pointing out these two papers. The one by Gyawali looks at the FDA approval of sunitinib for renal cell cancer and the one by Egilman about regulatory capture of the FDA. Regulatory capture is an extremely important issue but the Gyawali and Egilman papers are looking at this issue in the context of approving new drugs by an agency that has final authority over this matter. My paper examines two arms of an organization that recommends funding of already approved drugs and the recommendations can be ignored by the various federal, provincial and territorial funding bodies. Therefore, I don’t believe that the concept of regulatory capture is applicable here since pCODR is not a final decision maker.	
Would you be able to elaborate on the 1 case where the pCODR changed its recommendation from “no” to “yes – fund”? Was new evidence gathered? Did anything change in the data, or is this example the poster child of regulatory capture (refer to paragraph 1 of Egilman et al to see what I mean)?	The reason why pCODR changed its initial recommendation is now given along with the URL to the document containing the final decision.	267-270
I see that there are 37 preliminary recommendations and 46 final recommendations. How many final	The breakdown of the 37 preliminary recommendations between	204-209 258-260 280-291

recommendations were “do not funded”? If 1/3 of the recommendations are not funded, I would be curious about a subgroup analyses between clinicians who gave input for “fund” and “do not fund” recommendations, if that is possible. a. I ask because if you find that there is a greater proportion of FCOI at “funded” drug meetings, it can help identify the effect of FCOI on the panel recommendations.	fund/conditional funding and do not fund is now given. In addition, where it is possible to identify individual clinicians who gave comments, their comments have been analyzed based on their level of conflict (with the submitting company, with another company and no conflict) and the recommendation from pCODR and a 5th Table has been added. (The Methods section now includes a description of this analysis.)	
Are pCODR expert panelists allowed to have FCOI?	People on the pCODR panel are allowed to have FCOI but the focus of this study was on the FCOI of clinicians who made submissions to the panel and therefore the panelists FCOI were not analyzed.	
Do you have any policy recommendations that you would make for these pCODR meetings? For example, should it be required that the number of physicians who have FCOI be limited to 50% of speakers, since the discussion point you make shows that 46% of physicians were paid by industry in Canada.	I would definitely make recommendations about the composition of the pCODR expert panel since it is making recommendations but I’m not sure that limiting the number of people making submissions who have FCOI is practical. For example, it is not known in advance how many people or groups will be making submissions.	
Please include the start date of your sample in the Methods. I only see it in the abstract.	The start date has been added to the Methods	155
[Minor] The conclusion section of the abstract, you spelled conflicts “onflicts”.	The spelling error has been corrected.	76
Reviewer 2		
Professor Lexchin is addressing a vitally important topic - that of financial COI between oncologists, Industry, and regulatory agencies. This a study that is narrow in scope, identifying disclosed COI amongst neurologists submitting to the pCODR.	I thank the reviewer for the comment. Please note that I am identifying FCOI in clinicians treating cancer not neurologists.	
Structured Summary: Objectives: a slight introduction to the pCOD pCODR would be appropriate here to give the reader some context: "...make submission to the Canadian oncologic drug agency responsible for determining whether certain drugs should be publicly funded - the pCODR" for example. The objective is otherwise not clear unless you read a lot of the paper.	pCODR is not an agency it is an arm of the Canadian Agency for Drugs and Technology in Health. In addition, pCODR only makes recommendations it does not have the final say. However, the latter part of the sentence has been changed and now reads: “panCanadian Oncology Drug Review (pCODR), the arm of the Canadian Agency for Drugs and Technology in Health that recommends	33-34

	whether oncology drug-indications should be publicly funded."	
Outcomes: I would change the study period to the objective section and recommend demarcating the outcomes somehow to improve clarity: "The primary outcome is the number and nature of FCOI between oncologists and drug companies. Secondary outcomes include ..." As written is confusing and hard to read.	The following sentence has been added to the Objective section: "Final reports from pCODR published between October 2016 and February 2019 were examined." The material has been removed from the Outcomes section. The primary and secondary outcomes have been clarified and this section now reads: "The primary outcome is the number of submissions declaring FCOI with companies making the drug in question, other drug companies and with no declared FCOI. Secondary outcomes are the number of times where clinicians agreed and disagreed with preliminary recommendation from pCODR and the association between the distribution of individual clinicians' FCOI and pCODR's recommendations.	34-35 43-47
line 47. Would end sentence after pCODR and start Clinicians.	The change has been made.	49
Line 48 - unclear who the "They" is (pCODR or clinicians). Would change to "physicians" or somehow link to prior sentences. Also, as will be addressed below, I am not clear what "naming a company" means, if not declaring a FCOI or stock ownership. This needs to be flushed out better in the methods, and probably also here in the summary. "Naming" and "Declared" are not immediately self-evident terms.	"They" has been replaced by "Clinicians". The meaning of "declared" and "naming" has been clarified.	50-51
Line 51/52 (And elsewhere): might be clear with active voice : "Clinicians commented on 37 preliminary recommendations."	The change has been made.	66
Lines55. Should expand on what the p-value refers to. : "...with that recommendation. Clinicians were statistically more likely to disagree when the drug-funding indication was not approved, p<0.0001 Fisher Exact"	What the p-value refers to has been clarified.	69-71
Article Summary The first three bullet point in the strengths and limitations are descriptive of the study and not strengths or weaknesses. The second two are weaknesses.	I have adopted the reviewer's suggestion about one strength being that this is the first study of its kind. The wording of the second strength has been changed to emphasize that I have considered the entire universe of clinician submissions and not just a sample. One of the statements about a weakness has been	84-89

The strength is this is the first study of its kind. Weaknesses will be detailed below.	changed to make the point that these are voluntary and unsolicited submissions.	
Introduction: Would state upfront (line 104) whether this input is solicited or unsolicited (it is voluntary and unsolicited, as you explain later)	This change has been made.	143
Line 118 (and elsewhere throughout the manuscript), you should stick with FCOI or spell it out but be consistent	The change has been made here.	147
Methods It would be nice to have a background of how many reports were issues that did not receive submissions from a clinician. This contextualizes how frequently clinical submissions play a role in the agency's decisions.	The number of reports without submissions from clinicians has been noted in the Results.	223
Methods I am not clear why reconsiderations and funding for a different drug-indication are included. Do some physicians submit to both the initial consideration and the reconsideration? To the multiple drug-indications for the same drug? If so (and presumably the answer is yes), you need to address the methodological issue of double counting, which overestimates the relationships. You might think about presenting the data both ways if possible.	The reviewer raises a valid point, however pCODR views reconsiderations and funding for a different drug-indication as unique requests. Moreover, given that reconsiderations and funding for different drug-indications occur at different times from original submissions, the number and types of FCOI of clinicians and the companies with which they have their FCOI can change. Therefore, I don't believe that this is a case of double counting.	
Methods Line 137 and 138 is confusing due to punctuation - there should be parentheses around the (...e.g...consideration)	Brackets have been added.	168-169
Methods Again, I am confused in the Methods - how do companies get "named" if they are not part of a FCOI. This needs to be expanded.	The reviewer has not included the line numbers for the section that is confusing. Currently the sentence that the reviewer seems to be referring to reads "In addition, clinicians need to give the names of companies making the payments and the amounts of the payments" and the nature of the payments is given in the previous sentence. Therefore no change has been made.	
One issue not addressed (which is a weakness of the methods that limits external validity) is that the FCOI are only self-reported. There should be a discussion of literature demonstrating that clinicians consistently underreport COI voluntarily.	The reviewer is correct that FCOI is often not reported but I do not believe that the Methods section is the correct place to raise this issue. I have now discussed it in the Discussion section.	321-323

Another weakness that the author mentions but does not discuss at length is the fact that we cannot tell if these FCOI are relevant or not. There should be a more detailed discussion of the problem with not listing amounts. Small meal payments of $10 are diffferent than $100k consulting fees or stock options.	I am not sure what the reviewer means by "relevant". Even small payments, i.e., a $20 meal, have been shown to have an effect on prescribing, e.g., DeJong et al. Pharmaceutical industry-sponsored meals and physician prescribing patterns for Medicare beneficiaries. JAMA Internal Medicine 2016;176:1114-1122. No change has been made.	
Table 3 - again problematic because we do not know if there is double counting	I have responded to the issue about double counting above.	
It would be useful to know if The physicians who agreed with the recommendation tended to have COI with that company, and compare that with physicians who disagreed with the recommendations. Were any declared COI with companies that made competing drugs? This gets at the issue of whether the FCOI are relevant or not even if you do not have access to the dollar mounts.	The distribution of clinicians' FCOI and their association with funding recommendations (fund/conditional funding vs. do not fund) has been analyzed.	280-291
Discussion There has to be a discussion of the fact that the populations of submitting clinicians is self-selected and does not reflect the population of physicians as a whole. Clinicians with COI are more likely to submit. This explains the lower number (line 242) but is not addressed. Similarly, FDA advisory committees are picked randomly, rather than advisors self-selecting.	The Limitations section now notes that the results only apply to clinicians making voluntary, unsolicited submissions.	385-386
Discussion Line 251 - 256 : this part (and the rest of the discussion) would benefit from some more depth. for example, a suggestion of how things could be improved. Maybe Canada needs a mandatory reporting system for payments to physicians like the OP database to address the omissions. In general I found the discussion, like the introduction, to be a little cursory. To stress the importance of this paper the author should expand these sections discussed above	The last sentence in the Conclusion in the original version of this paper already called for the publication of details about clinicians' FCOI and this sentence has been strengthened.	403-405
Conclusion The sentence from line 320 to 323 is a limitation, not a conclusion.	I think that the sentence that the reviewer is referring to can be taken as a conclusion and I have left it in this section.	400-403 393-394 405-406

This section should probably also point out that there is too little information available publicly to assess 1) whether COI disclosures are accurate 2) whether submitting clinicians COI impact the decisions. Also the voluntary nature of the submissions leads to skewed commentary, so perhaps a panel of experts (with those with COI excluded) would be more balanced.	Information about the lack of any independent checking about the accuracy of FCOI declarations has been added to the Limitations section. A final sentence has been added making the suggestion that pCODR specifically ask clinicians without FCOI to make submissions.	
Reviewer 3		
Thank you for the opportunity to review your manuscript on financial conflict of interest of clinicians making submission to the panCanadian Oncology Drug Review: a descriptive study. This study focuses on a very important issue in medical research which is the influences of financial conflict of interest in research and in approval of new medications and technology.	I thank the reviewer for the comment.	
In the abstract is it not clear what is the primary outcome and which ones are secondary outcomes. Is this supposed to be a combined primary outcome? Please specify what is the primary outcome of the paper.	The primary and secondary outcomes have now been clearly stated.	43-47
In the abstract, in the conclusion section, there is a C missing for conflict.	The spelling error has been corrected.	76
Methods: were all reports for the study period that met the inclusion criteria included?	It is now clear that all reports that met the inclusion criteria were included.	154
Methods: was there a way to verify if clinicians were disclosing all their COI?	The Limitations section now notes that there was no independent checking about FCOI declarations.	393-394
Methods: please clarify if this is a voluntary service for clinicians to submit responses and recommendations, are they invited, or assigned these drug submissions?	It is now noted that submissions are voluntary and unsolicited.	143
Statistics: how did you determine that these were enough reports to find a difference? Was there a power analysis performed? Was the expected difference?	Power calculations were not done since all reports that met the inclusion criteria were included not just a sample.	
I want to point out that the majority of these drug submissions were approved or approved with some changes, and over 50% of members in the committee had a FCOI. There is a possibility that such a high approval rate is influenced by the presence of individuals with COI. There are studies in medical research which show that any COI will influence the study	This study looks at FCOI of people making submissions to pCODR. These people do not make the recommendations, those are made by the members of the pCODR committee. The FCOI of the pCODR committee members were not examined.	

outcomes, there is a high likelihood that this is the case here as well.		
For table 4, I think it would be helpful if you had the information of a subgroup analysis of how many clinicians with COI within a group agreed, or agreed in part, or disagree with the decision from the pCODR. Maybe if there is a difference if over 50% of the group had a COI versus other groups with less than 50% COI	The distribution of clinicians' FCOI and their association with funding recommendations (fund/conditional funding vs. do not fund) has been analyzed. I could not do an analysis comparing cases where less than 50% of clinicians who disagreed with a do not fund recommendation had a FCOI compared to cases where more than 50% had a FCOI as there were not enough cases to do any meaningful statistical analysis.	280-291