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Financial conflicts of interest of clinicians making submissions to the panCanadian Oncology Drug Review: a descriptive study

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28

Structured Summary

Objectives

This study examines financial conflict-of-interest (COI) of clinicians involved in oncology research and treatment who make submissions to the panCanadian Oncology Drug Review (pCODR) about whether drug-indications should be publicly funded.

Design

Descriptive study

Data sources

Website of panCanadian Oncology Drug Review

Interventions

None

Primary and secondary outcomes

Number of submissions declaring financial conflicts with all drug companies and companies making the drug in question from date of publication of final report - October 2016 to February 2019. Number of times where clinicians agreed and disagreed with preliminary recommendation from pCODR. The distribution of agreement/disagreement was compared for each of the three possible funding recommendations.

Results

There were 46 drug-indication reports from pCODR and clinicians made 261 submissions. They declared payments from companies 323 times and named 38 different companies a total of 500 times. Financial conflicts with drug companies were declared in 176 (66.3%) of all submissions. In 21 (45.7%) of the 46 drug-indications, 50% or more of the clinicians had a conflict with the company making the drug. There were 37 preliminary recommendations that clinicians commented on. In all 25 where pCODR recommended funding or conditional funding the clinicians either agreed or agreed in part. Twelve times pCODR recommended

that the drug-indication not be funded and 9 times clinicians disagreed with that recommendation $p < 0.0001$ (Fisher exact test).

Conclusion

Financial onflicts with pharmaceutical companies are widespread among experts making submissions to the pCODR.

Article Summary

Strengths and limitations of this study

- Descriptive study of financial conflict-of-interest (FCOI) of clinicians making submissions to the panCanadian Oncology Drug Review (pCODR).
- All clinician submissions evaluated from time of publication of final pCODR report - October 2016 to February 2019.
- Evaluation of whether clinicians agreed or disagreed with preliminary funding recommendations.
- Results only apply to oncology clinicians making submissions to pCODR.
- No data available to determine if FCOI affect clinicians' views about funding.

- **Acknowledgements**
- Catherine Oliver verified data extraction.

- **Competing Interests**
- In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and a second deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief for a law firm and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare.

- **Funding**
- This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

- **Data sharing statement**
- Data available from the Dryad Digital Repository: doi:10.5061/dryad.3k2c3s7.

- **Contributorship statement**
- JL came up with the idea for this study, gathered and analyzed the data and wrote the manuscript.

Introduction

Canada has no national drug formulary and as a result, the federal, provincial and territorial governments (except for Quebec) cooperate through the Canadian Agency for Drugs and Technology in Health (CADTH) to make recommendations about whether to fund unique drug-indication combinations. Specifically, the panCanadian Oncology Drug Review (pCODR), an arm of CADTH has been doing this for oncology products starting in January 2012 (1). Briefly, pCODR accepts applications from manufacturers and drug plans and then utilizes an expert panel (2, 3) that considers the clinical evidence, plus input from manufacturers, clinicians and patient groups in making its recommendations about whether the plans should list drugs for specific indications.

Since October 2016, pCODR has published input from registered clinicians defined as practising oncologists or physicians who treat cancer patients, oncology pharmacists and oncology nurses. “Oncologists or physicians who treat cancer patients can provide their input as an individual submission or jointly in a group submission. Oncology pharmacists and oncology nurses provide invaluable information on drug preparation and administration, and are eligible to provide input as part of a joint submission with a lead oncologist” (4). Part of the process of registering is completing a financial conflict of interest (FCOI) form (5). Once registered clinicians receive notifications via email of all upcoming reviews at pCODR. The email notification has information pertaining to the drug and indication under review, the link to the clinician input template, and the deadline date for submitting input.

In the United States, financial conflict of interest are associated with the voting patterns of members of Food and Drug Administration (FDA) advisory committees (6) but there has not

been any analysis of FCOIs of clinicians' input into funding recommendations. This study was undertaken to examine the FCOIs of clinicians making inputs into the pCODR process.

Methods

Source of data

Reports from pCODR are available at https://www.cadth.ca/pcodr/find-a-review. Reports were included if a final recommendation had been issued as of February 22, 2019 and if they included a submission from one or more clinicians. Applications from manufacturers where they were requesting a reconsideration of a previous decision or where they were requesting funding for a different drug-indications for the same drug were included and treated as separate applications. Besides allowing clinicians to make inputs to pCODR, they are also allowed to comment on preliminary decisions.

Information extracted from pCODR reports

From each report the following information was extracted: generic and brand name of drug, indication, company manufacturing the drug, preliminary and final recommendations about funding and whether the clinicians agreed, agreed in part or disagreed with the preliminary recommendation about funding – fund, fund based on conditions being fulfilled, e.g., the drug being cost effective or budgetary effects being taken into consideration and do not fund.

FCOI forms contain the name of the clinicians and ask them to declare payments received within the previous two years for one or more of ten types of activities: advisory role (advisory board and/or health technology advice), conference attendance, gifts, honoraria, royalties, program or operating funding (e.g., website), research/educational grants, sponsorship of events, travel grants and other. In addition, clinicians need to give the names of companies making the payments and the amounts of the payments. Clinicians also need to

list whether they have received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review and whether they have personal or commercial relationships either with a drug or health technology manufacturer (including such manufacturer's parent corporation, subsidiaries, affiliates and associated corporations) or other interest groups. Information on all of these categories was extracted and put into an Excel spreadsheet. The status of the clinician making the submission, i.e., physician, pharmacist, etc., is not contained in the FCOI statement and the amounts of money received from each company is blacked out.

Information was extracted by the author and verified by CO, a retired general practitioner. Disagreements were resolved by discussion.

Analyses of information from pCODR reports

Counts were made of the following: number of individual drug-indication reports from pCODR along with the number of clinicians making submissions per drug-indication, how many drug companies each clinician had a conflict with, whether they had a conflict with the company making the drug, a conflict with another drug company or had no declared conflicts with companies and the number of paid activities for drug companies each clinician reported when they made a submission. Based on this data, the number of submissions where a majority of clinicians had a conflict with any drug company and a conflict with the company making the drug was calculated. In addition, the number of different submissions from each clinician was totaled. Finally counts were made of the number of times a clinician reported stocks or options and personal or commercial relationships.

If a clinician or group of clinicians made a comment about the preliminary recommendation – agree, agree in part, disagree - the distribution of the type of comment was compared for each of the three possible funding recommendations.

Statistics

Agreement between views of clinicians about preliminary recommendations and the recommendations from pCODR were compared using Fisher's exact test. Prism 7.0d for Macintosh (GraphPad Software Inc.) was used for statistical testing.

Patients and ethics

No patients were involved in this study and all data was publicly available and therefore ethics approval was not necessary.

Results

There were reports for 46 drug-indications and clinicians made 261 submissions for these 46 drug-indications. Financial conflicts with drug companies were declared in 176 (66.3%) of all submissions; 119 times (45.6%) conflicts were with the company that made the drug under consideration, 52 times (19.9%) with another company and in 5 cases (1.9%) the name of the company was missing. In 78 cases (29.9%) clinicians did not declare any conflict and in 7 cases (2.7%) it was not known if a conflict existed because all of the information was missing (Table 1). In 33 out of the 46 (71.7%) drug-indications, 50% or more of the clinicians making a submission had a conflict with one or more drug companies and in 21 (45.7%) of the 46, 50% or more of the clinicians had a conflict with the company making the drug (Supplementary File 1).

Table 1: Number (percent) of clinicians declaring financial conflicts with companies and payments for activities

Status of conflict declared by clinician		Number of clinician submissions (percent all 261 submissions)	Number of times payments declared for activities (percent all payments)	Number of mentions of companies that clinicians had conflict with (percent all mentions)
Number of submissions with conflicts declared		173 (66.3)	323	500
	Conflict with company marketing drug	119 (45.6)	232 (71.8)	345 (69.0)
	Conflict with another company	52 (19.9)	81 (25.1)	155 (31.0)
	Conflict declared but company not named	5 (1.9)	10 (3.1)	--
Number of submissions declaring no conflict		78 (29.9)	0	0
Number of submissions where conflict declaration missing		7 (2.7)	--	--

Clinicians declared payments 323 times in the 10 different categories of activities; 232 (71.8%) were declared by clinicians with a conflict with the company making the drug and 81 (25.1%) were declared by clinicians who had conflicts with other companies (Table 1). Clinicians had conflicts with a mean of 2.9 drug companies and performed a mean of 1.9 activities for which they were paid. Payments for serving in an advisory role were declared 151 times and for the receipt of honoraria 88 times. Payments for other types of activities occurred less often (Table 2). Some clinicians declared receiving payments for different types of activities for different companies in different submissions.

Table 2: Number of different types of activities for which payments received

Type of activity	Advisory role	Conference attendance	Gifts	Honoraria	Program or operating funding	Research/educational grants	Royalties	Travel grants	Sponsorship of events	Other
Number of times payment received	151	16	0	88	2	32	0	10	17	7

The clinicians declaring conflicts named 38 different drug companies a total of 500 times ranging from Merck with 57 mentions to 8 companies with a single mention (Supplementary File 2). There were 5 declarations of stock ownership, all by the same person but information on this topic was missing in 31 out of 261 (11.9%) other submissions. There were 4 declarations of a personal or commercial relationship and information was missing 33 times out of 261 submissions (12.6%). Individual clinicians made between 1 and 10 separate submissions (Table 3).

Table 3: Number of individual submissions per clinician

Number of clinicians	Number of individual submissions
69	1
28	2
11	3
4	4
8	5
1	6
1	7
1	8
2	10

There were 37 preliminary recommendations from the pCODR that clinicians commented on. In all 25 cases where pCODR recommended funding or conditional funding the clinicians either agreed or agreed in part. Twelve times pCODR recommended that the drug-indication not be funded and 9 times clinicians disagreed with that recommendation, in one case they

agreed and in two cases they agreed in part (Table 4). The distribution of clinician responses in relation to the three funding recommendations from pCODR was statistically significantly different, $p < 0.0001$ (Fisher exact test). In one case the pCODR changed its preliminary do not fund recommendation to a final conditional fund recommendation.

Table 4: Clinician response to preliminary recommendation from panCanadian Oncology Drug Review

		Preliminary recommendation from panCanadian Oncology Drug Review		
		Fund	**Fund with conditions or criteria**	**Do not fund**
Response from clinicians	**Agrees**	1	17	1
	Agrees in part	0	7	2
	Disagrees	0	0	9

$p < 0.0001$, Fisher exact test

Discussion

The results of this study show that two-thirds of the clinicians who make submissions to the pCODR have FCOI with one or more pharmaceutical companies and almost half have FCOI with the company making the product that is being considered for public funding. The amount of money that clinicians received for their activities on behalf of the companies is not known as that information is blacked out on their FCOI declaration forms. In over 70% of the drug-indications being reviewed by the pCODR the majority of clinicians making submissions had conflicts. The largest number of activities for which physicians were paid was serving in an "advisory role", but exactly what this means is not clarified in the FCOI documents that are made public and it is possible that this term was interpreted differently by individual clinicians.

The level of COI revealed in this study is greater than that reported in a 2015 survey of Canadian physicians, where 46% said that they had been retained by a pharmaceutical

company in some capacity at some point in their career (7). It is also substantially larger than the level of FCOI of people serving on FDA advisory committees. These are committees convened by the FDA to vote on whether the FDA should approve new drug applications. An analysis of 379 meetings held over 15 years by 15 committees found that the median level of meeting "conflictedness" (percentage of individuals with a reported financial conflict of interest) was around 13% (range 2% to 29%). On average, committees reported that half of their meetings were attended by at least 1 person with a financial conflict (6).

An additional issue that this study identified was that there is missing information in a substantial number of FCOI declarations. Statements about stock ownership were not completed 11.9% of the time and those about a personal or commercial relationship were not completed 12.6% of the time. These omissions raise the question about whether these declarations are just pro forma, i.e., a piece of paper to be filled out and then ignored by the pCODR.

Two important questions are whether the conflicts held by the clinicians influenced their view about the drug-indication being considered and whether the conflicts influenced the final decision by the pCODR. pCODR does not publish the submissions from the clinicians but summarizes them in its reports and does not necessarily attribute views to individual people or groups in the case of a group submission. Therefore, when there are submissions from more than one individual clinician or groups of clinicians it is generally not possible to link views about a drug-indication (positive, neutral, negative) to the COIs of individuals or groups. However, the finding that 75% of the time when the preliminary recommendation of the pCODR was not to fund the drug, that some of the clinicians making submissions disagreed with the decision might indicate that their conflicts did determine their views about

the product. This suggestion needs to be tempered by a couple of points. First, clinicians may have held favourable views about the drug-indication before their relationship with a drug company started. Second, there can be a legitimate argument about whose views of the drug-indication were more accurate, those of the clinicians or those of the pCODR.

As to whether or not the clinicians had an influence on the final recommendation of the pCODR, it may be relevant that the pCODR only changed its recommendation from do not fund to fund with conditions in one out of the 9 cases where the clinicians disagreed with the preliminary decision. Removing all of the FDA advisory committee members with conflicts would have produced margins less favourable to the drug being considered in the majority of meetings, but this would not have changed whether the majority favoured or opposed the drug (8).

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) serves somewhat the same role as the pCODR (9). In making submissions to the PBAC, companies are able to recruit experts to provide an opinion about their drug and the sponsors have to provide a signed statement from each expert about their FCOIs (10). However, the FCOI documents from these experts are not publicly available so their degree of FCOI cannot be compared to that of experts giving input to pCODR.

The literature about whether disclosure of FCOI affects trust in individual doctors, the pharmaceutical industry and the healthcare system in general is mixed. A systematic review about the impact of disclosing financial ties in research and clinical care, found that patients believe that these influenced professional behaviour, decreased the quality of research evidence and should be disclosed (11). More recently, one study reported that when patients

knew believed that a gift relationship existed, they had lower levels of physician trust and higher rates of health care system distrust (12). While the level of payments affected perceptions of honesty and fidelity in individual physicians, viewing an online disclosure database did not affect patients' trust ratings for the medical profession or the pharmaceutical industry (13). Patient attitudes about FCOI in cancer research seems to be more forgiving. Most patients in cancer-research trials were not worried about FCOI between researchers and drug companies and would still have enrolled in the trial if they had known about these relationships (14). The only Canadian study on patients' attitudes found that public opinions on physician–pharmaceutical industry interactions differ depending on the scenario but suggested a significant level of concern regarding interactions involving direct financial benefit to physicians (15). Whether the conflicts held by clinicians leads to a public perception that the pCODR process is biased is a question that this current study cannot answer but should be the subject of further research.

Limitations

These results about the presence of conflicts only apply to clinicians making submissions about funding oncology drugs and the distribution of conflicts among other clinicians treating cancer who did not make a submission may be different. Similarly, the results may not apply to clinicians treating other diseases. Clinicians did not comment on 9 out of 46 preliminary recommendations. Whether they agreed with the final recommendation from pCODR is not known although it seems unlikely that they would have changed their views between the preliminary and final recommendations. The main strength of this study is that it looked at the entire population of recommendations from pCODR where clinicians made a submission about the drug-indication being considered.

Conclusion

Conflicts with pharmaceutical companies are widespread among experts making submissions to the pCODR. Information about how much experts are reimbursed for the activities that they undertake on behalf of companies is not disclosed by pCODR and attributing views to individual clinicians or groups of clinicians cannot be done since only summaries of the submissions are published. Publishing full submissions and the amounts that clinicians receive may help in determining any association between payments and clinicians' views.

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Supplementary File 1: Number (percent) of clinicians with drug company conflicts per drug-indication

Generic name*	Number of clinicians making submission	Number (percent) of clinicians with conflict with any company	Number (percent) of clinicians with conflict with company making drug
alecensaro	10	7 (70)	4 (40)
alectinib	4	4 (100)	0 (0)
alectinib	8	7 (87.5)	2 (25)
apalutamide	10	9 (90)	8 (80)
atezolizumab	8	6 (75)	1 (12.5)
avelumab	5	5 (100)	1 (20)
blinatumomab	2	1 (50)	1 (50)
blinatumomab	1	1 (100)	1 (100)
brentuximab vedotin	5	2 (40)	1 (20)
cabozantinib	3	2 (66.7)	0 (0)
carfilzomib	4	3 (75)	2 (50)
ceritinib	3	3 (100)	3 (100)
dabrafenib & trametinib	9	7 (77.8)	4 (44.4)†
daratumumab	8	7 (87.5)	6 (75)†
daratumumab	9	9 (100)	8 (88.9)
fulvestrant	4	1 (25)	0 (0)
ibrutinib	1	1 (100)	1 (100)
inotuzumab ozogamicin	5	2 (40)	2 (40)
irinotecan liposome	6	4 (66.7)	2 (33.3)
ixazomib	6	5 (83.3)*	5 (83.3)*
lenvatinib	5	5 (100)	4 (80)
lenvatinib	7	6 (85.7)	5 (71.4)
midostaurin	4	1 (25)	1 (25)
nivolumab	4	1 (25)	0 (0)
nivolumab	3	1 (33.3)	0 (0)
nivolumab & ipilimumab	5	5 (100)	5 (100)
nivolumab & ipilimumab	4	3 (75)	2 (50)
obinutuzumab	3	2 (66.7)	2 (66.7)
olaparib	7	6 (85.7)	5 (71.4)
olaparib	10	6 (60)	5 (50)
olaratumab	1	0 (0)	0 (0)
osimertinib	5	5 (100)	4 (80)
osimertinib	9	7 (77.8)	7 (77.8)
palbociclib	2	1 (50)	1 (50)
panitumumab	16	8 (50)†	6 (37.5)‡
pembrolizumab	7	6 (85.7)	3 (42.9)

pembrolizumab	6	4 (66.7)‡	2 (33.3)‡
pembrolizumab	10	4 (40)	3 (30)
pembrolizumab	4	2 (50)	1 (25)
pertuzumab-trastuzumab Combo Pack	4	1 (25)	1 (25)
regorafenib	7	3 (42.9)†	0 (0)‡
ribociclib	2	0 (0)	0 (0)
rituximab	1	0 (0)	0 (0)
trifluridine & tipiracil	12	3 (25)¶	2 (16.7)¶
vandetanib	1	1 (100)	1 (100)
venetoclax	11	8 (72.7)	7 (63.6)

*Some drugs were submitted for different indications or were submitted more than once for the same indication if they were initially refused funding.
†Information about conflicts missing for one clinician.
‡Information about conflicts missing for two clinicians.
¶ Information about conflicts missing for three clinicians.

Supplementary File 2: Number of times conflict with company mentioned

Name of company	Number of times mentioned
AbbVie	8
Amgen	20
Astellas	8
AstraZeneca	53
Away BioPharma	1
Bayer	6
Boehringer Ingelheim	44
Bristol-Myers Squibb	48
Canadian L	1
Celgene	17
Eisai	10
Eli Lilly	21
EMD Serono	3
ESMO	2
Ferring	2
Genomic H	1
Gilead	3
GlaxoSmithKline	3
Hoffman-LaRoche	34
Immunocore	2
Immunovaccine	1
Ipsen	4
Janssen	34
Johnson & Johnson	4
Karyopharm	1
Lundbeck	4
Merck	57
Merrimack	1
Millenium	2
Novartis	52
Otsuka	1
Pfizer	27
Sanofi Genzyme	8
Seattle Genetics	2
Shire	2
Taiho	2
Takeda	11
Vitalie	1

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Financial conflicts of interest of clinicians making submissions to the panCanadian Oncology Drug Review: a descriptive study

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Financial conflicts of interest of clinicians making submissions to the panCanadian Oncology Drug Review: a descriptive study

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Structured Summary

Objectives

This study examines financial conflict-of-interest (FCOI) of clinicians who made submissions to the panCanadian Oncology Drug Review (pCODR), the arm of the Canadian Agency for Drugs and Technology in Health that recommends whether oncology drug-indications should be publicly funded. Final reports from pCODR published between October 2016 and February 2019 were examined.

Design

Descriptive study

Data sources

Website of panCanadian Oncology Drug Review

Interventions

None

Primary and secondary outcomes

The primary outcome is the number of submissions declaring 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 funding recommendations.

Results

There were 46 drug-indication reports from pCODR. Clinicians made 261 submissions. Clinicians declared they received payments from companies 323 times and named 38 different companies making those payments a total of 500 times. Financial conflicts with drug companies were declared in 176 (66.3%) of all submissions. In 21 (45.7%) of the 46 drug-indications, 50% or more of the clinicians had a conflict with the company making the drug. Clinicians commented on 37 preliminary recommendations. In all 25 where pCODR

recommended funding or conditional funding the clinicians either agreed or agreed in part. pCODR recommended that the drug-indication not be funded 12 times and 9 times clinicians disagreed with that recommendation. The distribution of clinician responses was statistically significantly different depending on whether pCODR recommended funding/conditional funding or do not fund $p < 0.0001$ (Fisher exact test). The distribution of clinicians' FCOI differed depending on whether the recommendation was fund/conditional fund or do not fund $p = 0.027$ (Fisher exact test).

Conclusion

Financial conflicts with pharmaceutical companies are widespread among experts making submissions to the pCODR.

Article Summary

Strengths and limitations of this study

- This is the first study to examine financial conflict-of-interest (FCOI) of clinicians making submissions to the panCanadian Oncology Drug Review (pCODR).
- All clinician submissions were evaluated rather than just a sample of submissions.
- Results only apply to oncology clinicians making voluntary, unsolicited submissions to pCODR.
- No independent checking about accuracy of FCOI declarations.
- No data available to determine if FCOI affect clinicians' views about funding.

- **Acknowledgements**
- Catherine Oliver verified data extraction.

- **Competing Interests**
- In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and a second deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief for a law firm and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare.

- **Funding**
- This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

- **Data sharing statement**

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: https://doi.org/10.5061/dryad.qs41mg4.

- **Contributorship statement**
- JL came up with the idea for this study, gathered and analyzed the data and wrote the manuscript.

Introduction

Canada has no national drug formulary and as a result, the federal, provincial and territorial governments (except for Quebec) cooperate through the Canadian Agency for Drugs and Technology in Health (CADTH) to make recommendations about whether to fund unique drug-indication combinations. Specifically, the panCanadian Oncology Drug Review (pCODR), an arm of CADTH has been doing this for oncology products starting in January 2012 (1). Briefly, pCODR accepts applications from manufacturers and drug plans and then utilizes an expert panel (2, 3) that considers the clinical evidence, plus input from manufacturers and voluntary, unsolicited submissions from clinicians and patient groups in making its recommendations about whether the plans should list drugs for specific indications.

Since October 2016, pCODR has published input from registered clinicians defined as practising oncologists or physicians who treat cancer patients, oncology pharmacists and oncology nurses. “Oncologists or physicians who treat cancer patients can provide their input as an individual submission or jointly in a group submission. Oncology pharmacists and oncology nurses provide invaluable information on drug preparation and administration, and are eligible to provide input as part of a joint submission with a lead oncologist” (4). Part of the process of registering is completing a financial conflict of interest (FCOI) form (5). Once registered, clinicians receive notifications via email of all upcoming reviews at pCODR and can voluntarily make unsolicited submissions. The email notification has information pertaining to the drug and indication under review, the link to the clinician input template, and the deadline date for submitting input.

In the United States, FCOI are associated with the voting patterns of members of Food and Drug Administration (FDA) advisory committees (6) but there has not been any analysis of FCOIs of clinicians' input into funding recommendations. This study was undertaken to examine the distribution of FCOIs of clinicians making inputs into the pCODR process.

Methods

Source of data

Reports from pCODR are available at https://www.cadth.ca/pcodr/find-a-review. All reports were included if a final recommendation had been issued between October 2016 and February 22, 2019 and if they included a submission from one or more clinicians. Applications from manufacturers where they were requesting a reconsideration of a previous decision or where they were requesting funding for a different drug-indications for the same drug were included and treated as separate applications. Besides allowing clinicians to make inputs to pCODR, they are also allowed to comment on preliminary decisions.

Information extracted from pCODR reports

From each report the following information was extracted: generic and brand name of drug, indication, company manufacturing the drug, preliminary and final recommendations about funding and whether the clinicians agreed, agreed in part (agreed with the overall recommendation but requested modifications, e.g., expand patient group that should be covered) or disagreed with the preliminary recommendation about funding – fund, fund based on conditions being fulfilled (e.g., the drug being cost effective or budgetary effects being taken into consideration) and do not fund.

FCOI forms contain the name of the clinicians and ask them to declare payments received within the previous two years for one or more of ten types of activities: advisory role

(advisory board and/or health technology advice), conference attendance, gifts, honoraria, royalties, program or operating funding (e.g., website), research/educational grants, sponsorship of events, travel grants and other. In addition, clinicians need to give the names of companies making the payments and the amounts of the payments. Clinicians also need to list whether they have received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review and whether they have personal or commercial relationships either with a drug or health technology manufacturer (including such manufacturer's parent corporation, subsidiaries, affiliates and associated corporations) or other interest groups. Information on all of these categories was extracted and put into an Excel spreadsheet. The status of the clinician making the submission, i.e., physician, pharmacist, etc., is not contained in the FCOI statement and the amounts of money received from each company is blacked out.

Information was extracted by the author in March 2019 and verified by CO, a retired general practitioner. Disagreements were resolved by discussion.

Analyses of information from pCODR reports

Counts were made of the following: number of individual drug-indication reports from pCODR along with the number of clinicians making submissions per drug-indication, how many drug companies each clinician had a conflict with, whether they had a conflict with the company making the drug, a conflict with another drug company or had no declared conflicts with companies and the number of paid activities for drug companies each clinician reported when they made a submission. Based on this data, the number of submissions where a majority of clinicians had a conflict with any drug company and a conflict with the company making the drug was calculated. In addition, the number of different submissions from each

clinician was totaled. Finally counts were made of the number of times a clinician reported stocks or options and personal or commercial relationships.

If a clinician or group of clinicians made a comment about the preliminary recommendation – agree, agree in part, disagree - the distribution of the type of comment was compared for each of the three possible funding recommendations. Comments were sometimes made by a group of clinicians and in those cases it was not possible to identify specific people to determine their FCOI. Where clinicians submitting comments were named, their FCOI (with the submitting company, with another company or no FCOI) were recorded and the distribution of FCOI was compared depending on whether the recommendation was fund/conditional funding or do not fund.

Statistics

Agreement between views of clinicians about preliminary recommendations and the recommendations from pCODR and the distribution of the types of clinicians' FCOI between different funding recommendations were both analyzed using Fisher's exact test. Prism 7.0d for Macintosh (GraphPad Software Inc.) was used for statistical testing.

Patients and ethics

No patients were involved in this study and all data was publicly available and therefore ethics approval was not necessary.

Results

There were reports for 46 drug-indications and clinicians made 261 submissions for these 46 drug-indications. (An additional 10 reports did not include clinician submissions.) Financial

conflicts with drug companies were declared in 176 (66.3%) of all submissions; 119 times (45.6%) conflicts were with the company that made the drug under consideration, 52 times (19.9%) with another company and in 5 cases (1.9%) the name of the company was missing. In 78 cases (29.9%) clinicians did not declare any conflict and in 7 cases (2.7%) it was not known if a conflict existed because all of the information was missing (Table 1). In 33 out of the 46 (71.7%) drug-indications, 50% or more of the clinicians making a submission had a conflict with one or more drug companies and in 21 (45.7%) of the 46, 50% or more of the clinicians had a conflict with the company making the drug (Supplementary File 1).

Table 1: Number (percent) of clinicians declaring financial conflicts with companies and payments for activities

Status of conflict declared by clinician		**Number of clinician submissions (percent all 261 submissions)**	**Number of times payments declared for activities (percent all payments)**	**Number of mentions of companies that clinicians had conflict with (percent all mentions)**
Number of submissions with conflicts declared		173 (66.3)	323	500
	Conflict with company marketing drug	119 (45.6)	232 (71.8)	345 (69.0)
	Conflict with another company	52 (19.9)	81 (25.1)	155 (31.0)
	Conflict declared but company not named	5 (1.9)	10 (3.1)	--
Number of submissions declaring no conflict		78 (29.9)	0	0
Number of submissions where conflict declaration missing		7 (2.7)	--	--

Clinicians declared payments 323 times in the 10 different categories of activities; 232 (71.8%) were declared by clinicians with a conflict with the company making the drug and 81 (25.1%) were declared by clinicians who had conflicts with other companies (Table 1). Clinicians had conflicts with a mean of 2.9 drug companies and performed a mean of 1.9 activities for which they were paid. Payments for serving in an advisory role were declared 151 times and for the receipt of honoraria 88 times. Payments for other types of activities occurred less often (Table 2). Some clinicians declared receiving payments for different types of activities for different companies in different submissions.

Table 2: Number of different types of activities for which payments received

Type of activity	Advisory role	Conference attendance	Gifts	Honoraria	Program or operating funding	Research/educational grants	Royalties	Travel grants	Sponsorship of events	Other
Number of times payment received	151	16	0	88	2	32	0	10	17	7

The clinicians declaring conflicts named 38 different drug companies a total of 500 times ranging from Merck with 57 mentions to 8 companies with a single mention (Supplementary File 2). There were 5 declarations of stock ownership, all by the same person but information on this topic was missing in 31 out of 261 (11.9%) submissions. There were 4 declarations of a personal or commercial relationship and information was missing 33 times out of 261 submissions (12.6%). Individual clinicians made between 1 and 10 separate submissions (Table 3).

Table 3: Number of individual submissions per clinician

Number of clinicians	Number of individual submissions

69	1
28	2
11	3
4	4
8	5
1	6
1	7
1	8
2	10

There were 46 preliminary recommendations from pCODR (33 fund or conditional funding and 13 do not fund) and clinicians commented on 37 of these (25 fund or conditional funding and 12 do not fund). In all 25 cases where pCODR recommended funding or conditional funding the clinicians either agreed or agreed in part. Twelve times pCODR recommended that the drug-indication not be funded and 9 times clinicians disagreed with that recommendation, in one case they agreed and in two cases they agreed in part (Table 4). The distribution of clinician responses was statistically significantly different depending on whether pCODR recommended funding/conditional funding or do not fund $p < 0.0001$ (Fisher exact test). In one case the pCODR changed its preliminary do not fund recommendation to a final conditional funding recommendation as a result of a re-examination of the efficacy and safety information based on the feedback pCODR received from the company, clinicians and two patient groups (https://www.cadth.ca/sites/default/files/pcodr/pcodr_venetoclax_venclexta_cll_fn_rec.pdf).

Table 4: Clinician response to preliminary recommendation from panCanadian Oncology Drug Review

		Preliminary recommendation from panCanadian Oncology Drug Review		
		Fund	**Fund with conditions or criteria**	**Do not fund**
Response from clinicians	**Agrees**	1	17	1
	Agrees in part	0	7	2
	Disagrees	0	0	9

$p < 0.0001$, Fisher exact test

There were 40 clinicians who provided comments on 13 preliminary recommendations where it was possible to determine their FCOI. (Comments on the other 24 preliminary recommendations were made by a group of clinicians and names of individuals were not provided.) When the recommendation was fund or fund with conditions or criteria the majority of clinicians (18 out of 27) had no FCOI whereas when the recommendation was do not fund, the plurality of clinicians (6 out of 13) had a FCOI with the submitting company (Table 5). The distribution of FCOI of clinicians depending on the type of preliminary recommendation was statistically significantly different, p = 0.027 (Fisher exact test).

Table 5: Association between conflict of clinicians and preliminary funding recommendation

	Fund/Fund with conditions or criteria		
Agree/Agree in part	4	5	18
	Do not fund		
Disagree	6	4	3

p = 0.027, Fisher exact test

Discussion

The results of this study show that two-thirds of the clinicians who make submissions to the pCODR have FCOI with one or more pharmaceutical companies and almost half have FCOI with the company making the product that is being considered for public funding. The amount of money that clinicians received for their activities on behalf of the companies is not known as that information is blacked out on their FCOI declaration forms. In over 70% of the drug-indications being reviewed by the pCODR the majority of clinicians making submissions had conflicts. The largest number of activities for which physicians were paid was serving in an "advisory role", but exactly what this means is not clarified in the FCOI documents that are made public and it is possible that this term was interpreted differently by individual clinicians.

The level of COI revealed in this study is greater than that reported in a 2015 survey of Canadian physicians, where 46% said that they had been retained by a pharmaceutical company in some capacity at some point in their career (7). It is also substantially larger than the level of FCOI of people serving on FDA advisory committees. These are committees convened by the FDA to vote on whether the FDA should approve new drug applications. An analysis of 379 meetings held over 15 years by 15 committees found that the median level of meeting "conflictedness" (percentage of individuals with a reported FCOI) was around 13% (range 2% to 29%). On average, committees reported that half of their meetings were attended by at least 1 person with a financial conflict (6).

An additional issue that this study identified was that there is missing information in a substantial number of FCOI declarations. Statements about stock ownership were not completed 11.9% of the time and those about a personal or commercial relationship were not completed 12.6% of the time. These omissions raise the question about whether these declarations are just pro forma, i.e., a piece of paper to be filled out and then ignored by the pCODR. Moreover, there is evidence that declarations about FCOI are often omitted in medical journal articles (8, 9), in clinical practice guidelines (10, 11) and among people presenting at conferences (12).

Two important questions are whether the conflicts held by the clinicians influenced their view about the drug-indication being considered and whether the conflicts influenced the final decision by the pCODR. pCODR does not publish the submissions from the clinicians but summarizes them in its reports and does not necessarily attribute views to individual people or individual groups in the case where more than one individual or group makes a

submission. Therefore, when there are submissions from more than one individual clinician or more than one group of clinicians it is generally not possible to link views about a drug-indication (positive, neutral, negative) to the FCOIs. However, 75% of the time when the preliminary recommendation of the pCODR was not to fund the drug clinicians making submissions disagreed with the decision and most of the clinicians who disagreed with the recommendation declared a FCOI with the company making the product. These finding suggest that FCOI did determine clinicians' views about the product. This suggestion needs to be tempered by a couple of points. First, clinicians may have held favourable views about the drug-indication before their relationship with a drug company started. Second, there can be a legitimate argument about whose views of the drug-indication were more accurate, those of the clinicians or those of the pCODR.

As to whether or not the clinicians had an influence on the final recommendation of the pCODR, it may be relevant that the pCODR only changed its recommendation from do not fund to fund with conditions in one out of the 9 cases where the clinicians disagreed with the preliminary decision. Removing all of the FDA advisory committee members with conflicts would have produced margins less favourable to the drug being considered in the majority of meetings, but this would not have changed whether the majority favoured or opposed the drug (13).

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) serves somewhat the same role as the pCODR (14). In making submissions to the PBAC, companies are able to recruit experts to provide an opinion about their drug and the sponsors have to provide a signed statement from each expert about their FCOIs (15). However, the FCOI documents

from these experts are not publicly available so their degree of FCOI cannot be compared to that of experts giving input to pCODR.

The literature about whether disclosure of FCOI affects trust in individual doctors, the pharmaceutical industry and the healthcare system in general is mixed. A systematic review about the impact of disclosing financial ties in research and clinical care, found that patients believe that these influenced professional behaviour, decreased the quality of research evidence and should be disclosed (16). More recently, one study reported that when patients believed that a gift relationship existed, they had lower levels of physician trust and higher rates of health care system distrust (17). While the level of payments affected perceptions of honesty and fidelity in individual physicians, viewing an online disclosure database did not affect patients' trust ratings for the medical profession or the pharmaceutical industry (18). Patient attitudes about FCOI in cancer research seems to be more forgiving. Most patients in cancer-research trials were not worried about FCOI between researchers and drug companies and would still have enrolled in the trial if they had known about these relationships (19). The only Canadian study on patients' attitudes found that public opinions on physician–pharmaceutical industry interactions differ depending on the scenario but suggested a significant level of concern regarding interactions involving direct financial benefit to physicians (20). Whether the conflicts held by clinicians leads to a public perception that the pCODR process is biased is a question that this current study cannot answer but should be the subject of further research.

Limitations

These results about the presence of conflicts only apply to clinicians making voluntary, unsolicited submissions about funding oncology drugs and the distribution of conflicts among

other clinicians treating cancer who did not make a submission may be different. Similarly, the results may not apply to clinicians treating other diseases. Clinicians did not comment on 9 out of 46 preliminary recommendations. Whether they agreed with the final recommendation from pCODR is not known although it seems unlikely that they would have changed their views between the preliminary and final recommendations. FCOI declarations were not independently checked to see if there were undisclosed FCOI. The main strength of this study is that it looked at the entire population of recommendations from pCODR where clinicians made a submission about the drug-indication being considered.

Conclusion

Conflicts with pharmaceutical companies are widespread among experts making submissions to the pCODR. Information about how much experts are reimbursed for the activities that they undertake on behalf of companies is not disclosed by pCODR and attributing views to individual clinicians or groups of clinicians cannot be done since only summaries of the submissions are published. pCODR should publish full submissions, the exact amounts that clinicians receive and the names of companies making each of the payments, in order to help determine any association between payments and clinicians' views. pCODR could also consider specifically asking clinicians without any FCOI to make submissions.

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Supplementary File 1: Number (percent) of clinicians with drug company conflicts per drug-indication

Generic name*	Number of clinicians making submission	Number (percent) of clinicians with conflict with any company	Number (percent) of clinicians with conflict with company making drug
alecensaro	10	7 (70)	4 (40)
alectinib	4	4 (100)	0 (0)
alectinib	8	7 (87.5)	2 (25)
apalutamide	10	9 (90)	8 (80)
atezolizumab	8	6 (75)	1 (12.5)
avelumab	5	5 (100)	1 (20)
blinatumomab	2	1 (50)	1 (50)
blinatumomab	1	1 (100)	1 (100)
brentuximab vedotin	5	2 (40)	1 (20)
cabozantinib	3	2 (66.7)	0 (0)
carfilzomib	4	3 (75)	2 (50)
ceritinib	3	3 (100)	3 (100)
dabrafenib & trametinib	9	7 (77.8)	4 (44.4)†
daratumumab	8	7 (87.5)	6 (75)†
daratumumab	9	9 (100)	8 (88.9)
fulvestrant	4	1 (25)	0 (0)
ibrutinib	1	1 (100)	1 (100)
inotuzumab ozogamicin	5	2 (40)	2 (40)
irinotecan liposome	6	4 (66.7)	2 (33.3)
ixazomib	6	5 (83.3)*	5 (83.3)*
lenvatinib	5	5 (100)	4 (80)
lenvatinib	7	6 (85.7)	5 (71.4)
midostaurin	4	1 (25)	1 (25)
nivolumab	4	1 (25)	0 (0)
nivolumab	3	1 (33.3)	0 (0)
nivolumab & ipilimumab	5	5 (100)	5 (100)
nivolumab & ipilimumab	4	3 (75)	2 (50)
obinutuzumab	3	2 (66.7)	2 (66.7)
olaparib	7	6 (85.7)	5 (71.4)
olaparib	10	6 (60)	5 (50)
olaratumab	1	0 (0)	0 (0)
osimertinib	5	5 (100)	4 (80)
osimertinib	9	7 (77.8)	7 (77.8)
palbociclib	2	1 (50)	1 (50)
panitumumab	16	8 (50)†	6 (37.5)‡
pembrolizumab	7	6 (85.7)	3 (42.9)
pembrolizumab	6	4 (66.7)‡	2 (33.3)‡

pembrolizumab	10	4 (40)	3 (30)
pembrolizumab	4	2 (50)	1 (25)
pertuzumab-trastuzumab Combo Pack	4	1 (25)	1 (25)
regorafenib	7	3 (42.9)†	0 (0)‡
ribociclib	2	0 (0)	0 (0)
rituximab	1	0 (0)	0 (0)
trifluridine & tipiracil	12	3 (25)¶	2 (16.7)¶
vandetanib	1	1 (100)	1 (100)
venetoclax	11	8 (72.7)	7 (63.6)

*****Some drugs were submitted for different indications or were submitted more than once for the same indication if they were initially refused funding.
†Information about conflicts missing for one clinician.
‡Information about conflicts missing for two clinicians.
¶ Information about conflicts missing for three clinicians.

Supplementary File 2: Number of times conflict with company mentioned

Name of company	Number of times mentioned
AbbVie	8
Amgen	20
Astellas	8
AstraZeneca	53
Away BioPharma	1
Bayer	6
Boehringer Ingelheim	44
Bristol-Myers Squibb	48
Canadian L	1
Celgene	17
Eisai	10
Eli Lilly	21
EMD Serono	3
ESMO	2
Ferring	2
Genomic H	1
Gilead	3
GlaxoSmithKline	3
Hoffman-LaRoche	34
Immunocore	2
Immunovaccine	1
Ipsen	4
Janssen	34
Johnson & Johnson	4
Karyopharm	1
Lundbeck	4
Merck	57
Merrimack	1
Millenium	2
Novartis	52
Otsuka	1
Pfizer	27
Sanofi Genzyme	8
Seattle Genetics	2
Shire	2
Taiho	2
Takeda	11
Vitalie	1

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.