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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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Manuscripts

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3 1 **Financial conflicts of interest of clinicians making submissions to the panCanadian**
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5 2 **Oncology Drug Review: a descriptive study**
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29 **Structured Summary**

30 **Objectives**

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

34 **Design**

35 Descriptive study

36 **Data sources**

37 Website of panCanadian Oncology Drug Review

38 **Interventions**

39 None

40 **Primary and secondary outcomes**

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

46 **Results**

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

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3 54 that the drug-indication not be funded and 9 times clinicians disagreed with that
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5 55 recommendation $p < 0.0001$ (Fisher exact test).
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8 56 **Conclusion**

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10 57 Financial onflicts with pharmaceutical companies are widespread among experts making
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12 58 submissions to the pCODR.
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3 **60 Article Summary**
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6 *61 Strengths and limitations of this study*
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- 8 • Descriptive study of financial conflict-of-interest (FCOI) of clinicians making
9
10 submissions to the panCanadian Oncology Drug Review (pCODR).
11
12 • All clinician submissions evaluated from time of publication of final pCODR report -
13
14 October 2016 to February 2019.
15
16 • Evaluation of whether clinicians agreed or disagreed with preliminary funding
17
18 recommendations.
19
20 • Results only apply to oncology clinicians making submissions to pCODR.
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22 • No data available to determine if FCOI affect clinicians' views about funding.
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3 71 • **Acknowledgements**
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- 5 72 • Catherine Oliver verified data extraction.
6
7

8 73 • **Competing Interests**
9

- 10 74 • In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at
11
12 75 developing principles for conservative diagnosis (Gordon and Betty Moore Foundation)
13
14 76 and a second deciding what drugs should be provided free of charge by general
15
16 77 practitioners (Government of Canada, Ontario Supporting Patient Oriented Research
17
18 78 Support Unit and the St Michael's Hospital Foundation). He also received payment for
19
20 79 being on a panel at the American Diabetes Association, for a talk at the Toronto
21
22 80 Reference Library, for writing a brief for a law firm and from the Canadian Institutes of
23
24 81 Health Research for presenting at a workshop on conflict-of-interest in clinical practice
25
26 82 guidelines. He is currently a member of research groups that are receiving money from
27
28 83 the Canadian Institutes of Health Research and the Australian National Health and
29
30 84 Medical Research Council. He is member of the Foundation Board of Health Action
31
32 85 International and the Board of Canadian Doctors for Medicare.
33
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38 86 • **Funding**
39

- 40 87 • This research received no specific grant from any funding agency in the public,
41
42 88 commercial or not-for profit sectors.
43
44

45 89 • **Data sharing statement**
46

- 47 90 • Data available from the Dryad Digital Repository: doi:10.5061/dryad.3k2c3s7.
48
49 91

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51 92 • **Contributorship statement**
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- 53 93 • JL came up with the idea for this study, gathered and analyzed the data and wrote the
54
55 94 manuscript.
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96

97 Introduction

98 Canada has no national drug formulary and as a result, the federal, provincial and territorial
99 governments (except for Quebec) cooperate through the Canadian Agency for Drugs and
100 Technology in Health (CADTH) to make recommendations about whether to fund unique
101 drug-indication combinations. Specifically, the panCanadian Oncology Drug Review
102 (pCODR), an arm of CADTH has been doing this for oncology products starting in January
103 2012 (1). Briefly, pCODR accepts applications from manufacturers and drug plans and then
104 utilizes an expert panel (2, 3) that considers the clinical evidence, plus input from
105 manufacturers, clinicians and patient groups in making its recommendations about whether
106 the plans should list drugs for specific indications.

107

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

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

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2
3 120 been any analysis of FCOIs of clinicians' input into funding recommendations. This study
4
5 121 was undertaken to examine the FCOIs of clinicians making inputs into the pCODR process.
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10 123 **Methods**

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12 124 *Source of data*

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14 125 Reports from pCODR are available at <https://www.cadth.ca/pcodr/find-a-review>. Reports
15
16 126 were included if a final recommendation had been issued as of February 22, 2019 and if they
17
18 127 included a submission from one or more clinicians. Applications from manufacturers where
19
20 128 they were requesting a reconsideration of a previous decision or where they were requesting
21
22 129 funding for a different drug-indications for the same drug were included and treated as
23
24 130 separate applications. Besides allowing clinicians to make inputs to pCODR, they are also
25
26 131 allowed to comment on preliminary decisions.
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33 133 *Information extracted from pCODR reports*

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35 134 From each report the following information was extracted: generic and brand name of drug,
36
37 135 indication, company manufacturing the drug, preliminary and final recommendations about
38
39 136 funding and whether the clinicians agreed, agreed in part or disagreed with the preliminary
40
41 137 recommendation about funding – fund, fund based on conditions being fulfilled, e.g., the
42
43 138 drug being cost effective or budgetary effects being taken into consideration and do not fund.
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48 139 FCOI forms contain the name of the clinicians and ask them to declare payments received
49
50 140 within the previous two years for one or more of ten types of activities: advisory role
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52 141 (advisory board and/or health technology advice), conference attendance, gifts, honoraria,
53
54 142 royalties, program or operating funding (e.g., website), research/educational grants,
55
56 143 sponsorship of events, travel grants and other. In addition, clinicians need to give the names
57
58 144 of companies making the payments and the amounts of the payments. Clinicians also need to
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3 145 list whether they have received or are in possession of stocks or options of more than \$10,000
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5 146 (excluding mutual funds) for organizations that may have a direct or indirect interest in the
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7 147 drug under review and whether they have personal or commercial relationships either with a
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9 148 drug or health technology manufacturer (including such manufacturer's parent corporation,
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11 149 subsidiaries, affiliates and associated corporations) or other interest groups. Information on
12
13 150 all of these categories was extracted and put into an Excel spreadsheet. The status of the
14
15 151 clinician making the submission, i.e., physician, pharmacist, etc., is not contained in the
16
17 152 FCOI statement and the amounts of money received from each company is blacked out.
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23 153 Information was extracted by the author and verified by CO, a retired general practitioner.
24
25 154 Disagreements were resolved by discussion.
26
27

28 155 *Analyses of information from pCODR reports*

29
30 156 Counts were made of the following: number of individual drug-indication reports from
31
32 157 pCODR along with the number of clinicians making submissions per drug-indication, how
33
34 158 many drug companies each clinician had a conflict with, whether they had a conflict with the
35
36 159 company making the drug, a conflict with another drug company or had no declared conflicts
37
38 160 with companies and the number of paid activities for drug companies each clinician reported
39
40 161 when they made a submission. Based on this data, the number of submissions where a
41
42 162 majority of clinicians had a conflict with any drug company and a conflict with the company
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44 163 making the drug was calculated. In addition, the number of different submissions from each
45
46 164 clinician was totaled. Finally counts were made of the number of times a clinician reported
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48 165 stocks or options and personal or commercial relationships.
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3 167 If a clinician or group of clinicians made a comment about the preliminary recommendation –
4
5 168 agree, agree in part, disagree - the distribution of the type of comment was compared for each
6
7
8 169 of the three possible funding recommendations.
9

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11
12 171 *Statistics*

13
14 172 Agreement between views of clinicians about preliminary recommendations and the
15
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17 173 recommendations from pCODR were compared using Fisher's exact test. Prism 7.0d for
18
19 174 Macintosh (GraphPad Software Inc.) was used for statistical testing.
20

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24 176 *Patients and ethics*

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26 177 No patients were involved in this study and all data was publicly available and therefore
27
28 178 ethics approval was not necessary.
29

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33 180 **Results**

34
35 181 There were reports for 46 drug-indications and clinicians made 261 submissions for these 46
36
37 182 drug-indications. Financial conflicts with drug companies were declared in 176 (66.3%) of all
38
39
40 183 submissions; 119 times (45.6%) conflicts were with the company that made the drug under
41
42 184 consideration, 52 times (19.9%) with another company and in 5 cases (1.9%) the name of the
43
44 185 company was missing. In 78 cases (29.9%) clinicians did not declare any conflict and in 7
45
46 186 cases (2.7%) it was not known if a conflict existed because all of the information was missing
47
48 187 (Table 1). In 33 out of the 46 (71.7%) drug-indications, 50% or more of the clinicians making
49
50 188 a submission had a conflict with one or more drug companies and in 21 (45.7%) of the 46,
51
52 189 50% or more of the clinicians had a conflict with the company making the drug
53
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55 190 (Supplementary File 1).
56

57
58 191 **Table 1: Number (percent) of clinicians declaring financial conflicts with companies and**
59
60 192 **payments for activities**

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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)	--	--

194

195 Clinicians declared payments 323 times in the 10 different categories of activities; 232
 196 (71.8%) were declared by clinicians with a conflict with the company making the drug and
 197 81 (25.1%) were declared by clinicians who had conflicts with other companies (Table 1).
 198 Clinicians had conflicts with a mean of 2.9 drug companies and performed a mean of 1.9
 199 activities for which they were paid. Payments for serving in an advisory role were declared
 200 151 times and for the receipt of honoraria 88 times. Payments for other types of activities
 201 occurred less often (Table 2). Some clinicians declared receiving payments for different types
 202 of activities for different companies in different submissions.

203

204 **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

205

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

213 **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

214

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

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

223 **Table 4: Clinician response to preliminary recommendation from panCanadian**
 224 **Oncology Drug Review**
 225

		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

226
 227 $p < 0.0001$, Fisher exact test
 228

229 Discussion

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

240

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

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3 243 company in some capacity at some point in their career (7). It is also substantially larger than
4
5 244 the level of FCOI of people serving on FDA advisory committees. These are committees
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8 245 convened by the FDA to vote on whether the FDA should approve new drug applications. An
9
10 246 analysis of 379 meetings held over 15 years by 15 committees found that the median level of
11
12 247 meeting “conflictedness” (percentage of individuals with a reported financial conflict of
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15 248 interest) was around 13% (range 2% to 29%). On average, committees reported that half of
16
17 249 their meetings were attended by at least 1 person with a financial conflict (6).

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20
21 251 An additional issue that this study identified was that there is missing information in a
22
23 252 substantial number of FCOI declarations. Statements about stock ownership were not
24
25 253 completed 11.9% of the time and those about a personal or commercial relationship were not
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27 254 completed 12.6% of the time. These omissions raise the question about whether these
28
29 255 declarations are just pro forma, i.e., a piece of paper to be filled out and then ignored by the
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31 256 pCODR.

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37 258 Two important questions are whether the conflicts held by the clinicians influenced their
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39 259 view about the drug-indication being considered and whether the conflicts influenced the
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41 260 final decision by the pCODR. pCODR does not publish the submissions from the clinicians
42
43 261 but summarizes them in its reports and does not necessarily attribute views to individual
44
45 262 people or groups in the case of a group submission. Therefore, when there are submissions
46
47 263 from more than one individual clinician or groups of clinicians it is generally not possible to
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49 264 link views about a drug-indication (positive, neutral, negative) to the COIs of individuals or
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51 265 groups. However, the finding that 75% of the time when the preliminary recommendation of
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53 266 the pCODR was not to fund the drug, that some of the clinicians making submissions
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55 267 disagreed with the decision might indicate that their conflicts did determine their views about
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3 268 the product. This suggestion needs to be tempered by a couple of points. First, clinicians may
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5 269 have held favourable views about the drug-indication before their relationship with a drug
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8 270 company started. Second, there can be a legitimate argument about whose views of the drug-
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10 271 indication were more accurate, those of the clinicians or those of the pCODR.

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14 273 As to whether or not the clinicians had an influence on the final recommendation of the
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16 274 pCODR, it may be relevant that the pCODR only changed its recommendation from do not
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18 275 fund to fund with conditions in one out of the 9 cases where the clinicians disagreed with the
19
20 276 preliminary decision. Removing all of the FDA advisory committee members with conflicts
21
22 277 would have produced margins less favourable to the drug being considered in the majority of
23
24 278 meetings, but this would not have changed whether the majority favoured or opposed the
25
26 279 drug (8).

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33 281 In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) serves somewhat the
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35 282 same role as the pCODR (9). In making submissions to the PBAC, companies are able to
36
37 283 recruit experts to provide an opinion about their drug and the sponsors have to provide a
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39 284 signed statement from each expert about their FCOIs (10). However, the FCOI documents
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41 285 from these experts are not publicly available so their degree of FCOI cannot be compared to
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43 286 that of experts giving input to pCODR.

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49 288 The literature about whether disclosure of FCOI affects trust in individual doctors, the
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51 289 pharmaceutical industry and the healthcare system in general is mixed. A systematic review
52
53 290 about the impact of disclosing financial ties in research and clinical care, found that patients
54
55 291 believe that these influenced professional behaviour, decreased the quality of research
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57 292 evidence and should be disclosed (11). More recently, one study reported that when patients
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3 293 knew believed that a gift relationship existed, they had lower levels of physician trust and
4
5 294 higher rates of health care system distrust (12). While the level of payments affected
6
7 295 perceptions of honesty and fidelity in individual physicians, viewing an online disclosure
8
9 296 database did not affect patients' trust ratings for the medical profession or the pharmaceutical
10
11 297 industry (13). Patient attitudes about FCOI in cancer research seems to be more forgiving.
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13 298 Most patients in cancer-research trials were not worried about FCOI between
14
15 299 researchers and drug companies and would still have enrolled in the trial if they had known
16
17 300 about these relationships (14). The only Canadian study on patients' attitudes found that
18
19 301 public opinions on physician–pharmaceutical industry interactions differ depending on the
20
21 302 scenario but suggested a significant level of concern regarding interactions involving direct
22
23 303 financial benefit to physicians (15). Whether the conflicts held by clinicians leads to a public
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25 304 perception that the pCODR process is biased is a question that this current study cannot
26
27 305 answer but should be the subject of further research.
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306

307 *Limitations*

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

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1
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3 318 **Conclusion**
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5 319 Conflicts with pharmaceutical companies are widespread among experts making submissions
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7 320 to the pCODR. Information about how much experts are reimbursed for the activities that
8
9 321 they undertake on behalf of companies is not disclosed by pCODR and attributing views to
10
11 322 individual clinicians or groups of clinicians cannot be done since only summaries of the
12
13 323 submissions are published. Publishing full submissions and the amounts that clinicians
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15 324 receive may help in determining any association between payments and clinicians' views.
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327 **References**

- 328 1. CADTH. About the pan-Canadian Oncology Drug Review (pCODR): CADTH; 2019
329 [Available from: <https://www.cadth.ca/pcodr/about-pcodr>.
- 330 2. pCODR expert review committee terms of reference: CADTH; 2016 [updated May.
331 Available from:
332 [https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20C](https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_expertreviewcom_tor.pdf)
333 [ommittee%20%28pERC%29/pcodr_expertreviewcom_tor.pdf](https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_expertreviewcom_tor.pdf).
- 334 3. CADTH Common Drug Review. Procedure for the CADTH Common Drug Review:
335 CADTH; 2014 [updated August. Available from:
336 https://www.cadth.ca/sites/default/files/cdr/process/Procedure_for_CADTH_CDR.pdf.
- 337 4. CADTH. pCODR clinician input and feedback: CADTH; 2019 [Available from:
338 <https://cadth.ca/pcodr/clinician-input-and-feedback>.
- 339 5. CADTH. Frequently asked questions: clinician input and feedback for the CADTH
340 pCODR program: CADTH; no date [Available from:
341 <https://cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pCO>
342 [DR_ClinicianInputFeedbackFAQ.pdf](https://cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pCODR_ClinicianInputFeedbackFAQ.pdf).
- 343 6. Pham-Kanter G. Revisiting financial conflicts of interest in FDA advisory committees.
344 *Milbank Quarterly*. 2014;92:446-70.
- 345 7. Leslie C. Relationship between MDs and pharma changing. *The Medical Post*. 2015
346 September 15.
- 347 8. Lurie P, Almeida C, Stine N, Stine A, Wolfe S. Financial conflict of interest disclosure
348 and voting patterns at Food and Drug Administration drug advisory committee meetings.
349 *JAMA*. 2006;295:1921-8.
- 350 9. Pharmaceutical Benefits Scheme. Pharmaceutical Benefits Advisory Committee
351 (PBAC) membership: Australian Government Department of Health; 2019 [Available from:
352 <http://www.pbs.gov.au/info/industry/listing/participants/pbac>.
- 353 10. Pharmaceutical Benefits Scheme. Guidelines: Appendix 1 expert opinion: Australian
354 Government Department of Health; 2019 [Available from:
355 <https://pbac.pbs.gov.au/appendixes/appendix-1-expert-opinion.html>.
- 356 11. Licurse A, Barber E, Joffe S, Gross C. The impact of disclosing financial ties in research
357 and clinical care: a systematic review. *Archives of Internal Medicine*. 2010;170:675-82.
- 358 12. Grande D, Shea J, Armstrong K. Pharmaceutical industry gifts to physicians: patient
359 beliefs and trust in physicians and the health care system. *Journal of General Internal*
360 *Medicine*. 2011;27:274-9.
- 361 13. Hwong A, Sah S, Lehmann L. The effects of public disclosure of industry payments to
362 physicians on patient trust: a randomized experiment. *Journal of General Internal Medicine*.
363 2017;32:1186-92.
- 364 14. Hampson L, Agrawal M, Joffe S, Gross C, Verter J, Emanuel E. Patients' views on
365 financial conflicts of interest in cancer research trials. *New England Journal of Medicine*.
366 2006;355:2330-7.
- 367 15. Holbrook A, Lexchin J, Pullenayegum E, Campbell C, Marlow B, Troyan S, et al. What
368 do Canadians think about physician-pharmaceutical industry interactions? *Health Policy*.
369 2013;112:255-63.

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.

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3 **Supplementary File 2: Number of times conflict with company mentioned**
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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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 (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	7-8
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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030750.R1
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Primary Subject Heading:	Health policy
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	financial conflict-of-interest, panCanadian Oncology Drug Review, clinician, medicines, funding recommendations

SCHOLARONE™
Manuscripts

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3 1 **Financial conflicts of interest of clinicians making submissions to the panCanadian**
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5 2 **Oncology Drug Review: a descriptive study**
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8 3
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46 23 **Key words:**

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48 24 financial conflict-of-interest, panCanadian Oncology Drug Review, clinician, medicines,
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50 25 funding recommendation

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52 26 **Word count:**

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For peer review only

29 **Structured Summary**

30 **Objectives**

31 This study examines financial conflict-of-interest (FCOI) of clinicians who made
32 submissions to the panCanadian Oncology Drug Review (pCODR), the arm of the Canadian
33 Agency for Drugs and Technology in Health that recommends whether oncology drug-
34 indications should be publicly funded. Final reports from pCODR published between October
35 2016 and February 2019 were examined.

36 **Design**

37 Descriptive study

38 **Data sources**

39 Website of panCanadian Oncology Drug Review

40 **Interventions**

41 None

42 **Primary and secondary outcomes**

43 The primary outcome is the number of submissions declaring FCOI. Secondary outcomes are
44 the number of times where clinicians agreed and disagreed with preliminary recommendation
45 from pCODR and the association between the distribution of individual clinicians' FCOI and
46 pCODR's funding recommendations.

47 **Results**

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

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3 54 recommended funding or conditional funding the clinicians either agreed or agreed in part.
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5 55 pCODR recommended that the drug-indication not be funded 12 times and 9 times clinicians
6
7 56 disagreed with that recommendation. The distribution of clinician responses was statistically
8
9 57 significantly different depending on whether pCODR recommended funding/conditional
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11 58 funding or do not fund $p < 0.0001$ (Fisher exact test). The distribution of clinicians' FCOI
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13 59 differed depending on whether the recommendation was fund/conditional fund or do not fund
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15 60 $p = 0.027$ (Fisher exact test).
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19 **Conclusion**

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21 62 Financial conflicts with pharmaceutical companies are widespread among experts making
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23 63 submissions to the pCODR.
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3 **65 Article Summary**
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5 **66 *Strengths and limitations of this study***
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- 7
8 **67** • This is the first study to examine financial conflict-of-interest (FCOI) of clinicians
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10 **68** making submissions to the panCanadian Oncology Drug Review (pCODR).
11
12 **69** • All clinician submissions were evaluated rather than just a sample of submissions.
13
14 **70** • Results only apply to oncology clinicians making voluntary, unsolicited submissions to
15
16 **71** pCODR.
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18 **72** • No independent checking about accuracy of FCOI declarations.
19
20 **73** • No data available to determine if FCOI affect clinicians' views about funding.
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24 **74**

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3 75 • **Acknowledgements**
4

- 5 76 • Catherine Oliver verified data extraction.
6
7

8 77 • **Competing Interests**
9

- 10 78 • In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at
11
12 79 developing principles for conservative diagnosis (Gordon and Betty Moore Foundation)
13
14
15 80 and a second deciding what drugs should be provided free of charge by general
16
17 81 practitioners (Government of Canada, Ontario Supporting Patient Oriented Research
18
19 82 Support Unit and the St Michael's Hospital Foundation). He also received payment for
20
21 83 being on a panel at the American Diabetes Association, for a talk at the Toronto
22
23 84 Reference Library, for writing a brief for a law firm and from the Canadian Institutes of
24
25 85 Health Research for presenting at a workshop on conflict-of-interest in clinical practice
26
27 86 guidelines. He is currently a member of research groups that are receiving money from
28
29 87 the Canadian Institutes of Health Research and the Australian National Health and
30
31 88 Medical Research Council. He is member of the Foundation Board of Health Action
32
33 89 International and the Board of Canadian Doctors for Medicare.
34
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37
38 90 • **Funding**
39

- 40 91 • This research received no specific grant from any funding agency in the public,
41
42 92 commercial or not-for profit sectors.
43
44

45 93 • **Data sharing statement**
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- 47 94 Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi:
48 95 <https://doi.org/10.5061/dryad.qs41mg4>.
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51 97 • **Contributorship statement**
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- 53 98 • JL came up with the idea for this study, gathered and analyzed the data and wrote the
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55 99 manuscript.
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101

102 **Introduction**

103 Canada has no national drug formulary and as a result, the federal, provincial and territorial
104 governments (except for Quebec) cooperate through the Canadian Agency for Drugs and
105 Technology in Health (CADTH) to make recommendations about whether to fund unique
106 drug-indication combinations. Specifically, the panCanadian Oncology Drug Review
107 (pCODR), an arm of CADTH has been doing this for oncology products starting in January
108 2012 (1). Briefly, pCODR accepts applications from manufacturers and drug plans and then
109 utilizes an expert panel (2, 3) that considers the clinical evidence, plus input from
110 manufacturers and voluntary, unsolicited submissions from clinicians and patient groups in
111 making its recommendations about whether the plans should list drugs for specific
112 indications.

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

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3 125 In the United States, FCOI are associated with the voting patterns of members of Food and
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5 126 Drug Administration (FDA) advisory committees (6) but there has not been any analysis of
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7 127 FCOIs of clinicians' input into funding recommendations. This study was undertaken to
8
9 128 examine the distribution of FCOIs of clinicians making inputs into the pCODR process.
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14 130 **Methods**

15 131 *Source of data*

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17 132 Reports from pCODR are available at <https://www.cadth.ca/pcodr/find-a-review>. All reports
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19 133 were included if a final recommendation had been issued between October 2016 and
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21 134 February 22, 2019 and if they included a submission from one or more clinicians.
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24 135 Applications from manufacturers where they were requesting a reconsideration of a previous
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26 136 decision or where they were requesting funding for a different drug-indications for the same
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28 137 drug were included and treated as separate applications. Besides allowing clinicians to make
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30 138 inputs to pCODR, they are also allowed to comment on preliminary decisions.
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33 140 *Information extracted from pCODR reports*

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35 141 From each report the following information was extracted: generic and brand name of drug,
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37 142 indication, company manufacturing the drug, preliminary and final recommendations about
38
39 143 funding and whether the clinicians agreed, agreed in part (agreed with the overall
40
41 144 recommendation but requested modifications, e.g., expand patient group that should be
42
43 145 covered) or disagreed with the preliminary recommendation about funding – fund, fund based
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45 146 on conditions being fulfilled (e.g., the drug being cost effective or budgetary effects being
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47 147 taken into consideration) and do not fund.
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51 148 FCOI forms contain the name of the clinicians and ask them to declare payments received
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53 149 within the previous two years for one or more of ten types of activities: advisory role
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3 150 (advisory board and/or health technology advice), conference attendance, gifts, honoraria,
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5 151 royalties, program or operating funding (e.g., website), research/educational grants,
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7 152 sponsorship of events, travel grants and other. In addition, clinicians need to give the names
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9 153 of companies making the payments and the amounts of the payments. Clinicians also need to
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11 154 list whether they have received or are in possession of stocks or options of more than \$10,000
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13 155 (excluding mutual funds) for organizations that may have a direct or indirect interest in the
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15 156 drug under review and whether they have personal or commercial relationships either with a
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17 157 drug or health technology manufacturer (including such manufacturer's parent corporation,
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19 158 subsidiaries, affiliates and associated corporations) or other interest groups. Information on
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21 159 all of these categories was extracted and put into an Excel spreadsheet. The status of the
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23 160 clinician making the submission, i.e., physician, pharmacist, etc., is not contained in the
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25 161 FCOI statement and the amounts of money received from each company is blacked out.
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32 162 Information was extracted by the author in March 2019 and verified by CO, a retired general
33
34 163 practitioner. Disagreements were resolved by discussion.
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38 164 *Analyses of information from pCODR reports*

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40 165 Counts were made of the following: number of individual drug-indication reports from
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42 166 pCODR along with the number of clinicians making submissions per drug-indication, how
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44 167 many drug companies each clinician had a conflict with, whether they had a conflict with the
45
46 168 company making the drug, a conflict with another drug company or had no declared conflicts
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48 169 with companies and the number of paid activities for drug companies each clinician reported
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50 170 when they made a submission. Based on this data, the number of submissions where a
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52 171 majority of clinicians had a conflict with any drug company and a conflict with the company
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54 172 making the drug was calculated. In addition, the number of different submissions from each
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3 173 clinician was totaled. Finally counts were made of the number of times a clinician reported
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5 174 stocks or options and personal or commercial relationships.
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10 176 If a clinician or group of clinicians made a comment about the preliminary recommendation –
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12 177 agree, agree in part, disagree - the distribution of the type of comment was compared for each
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14 178 of the three possible funding recommendations. Comments were sometimes made by a group
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17 179 of clinicians and in those cases it was not possible to identify specific people to determine
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19 180 their FCOI. Where clinicians submitting comments were named, their FCOI (with the
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21 181 submitting company, with another company or no FCOI) were recorded and the distribution
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24 182 of FCOI was compared depending on whether the recommendation was fund/conditional
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26 183 funding or do not fund.
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185 *Statistics*

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

190

191 *Patients and ethics*

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

194

195 **Results**

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

198 conflicts with drug companies were declared in 176 (66.3%) of all submissions; 119 times
 199 (45.6%) conflicts were with the company that made the drug under consideration, 52 times
 200 (19.9%) with another company and in 5 cases (1.9%) the name of the company was missing.
 201 In 78 cases (29.9%) clinicians did not declare any conflict and in 7 cases (2.7%) it was not
 202 known if a conflict existed because all of the information was missing (Table 1). In 33 out of
 203 the 46 (71.7%) drug-indications, 50% or more of the clinicians making a submission had a
 204 conflict with one or more drug companies and in 21 (45.7%) of the 46, 50% or more of the
 205 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)	--	--

209

210 Clinicians declared payments 323 times in the 10 different categories of activities; 232
 211 (71.8%) were declared by clinicians with a conflict with the company making the drug and
 212 81 (25.1%) were declared by clinicians who had conflicts with other companies (Table 1).
 213 Clinicians had conflicts with a mean of 2.9 drug companies and performed a mean of 1.9
 214 activities for which they were paid. Payments for serving in an advisory role were declared
 215 151 times and for the receipt of honoraria 88 times. Payments for other types of activities
 216 occurred less often (Table 2). Some clinicians declared receiving payments for different types
 217 of activities for different companies in different submissions.

218

219 **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

220

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

228 **Table 3: Number of individual submissions per clinician**

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

229

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

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

245

		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

246

247 $p < 0.0001$, Fisher exact test

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

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

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

258
 259 $p = 0.027$, Fisher exact test

262 Discussion

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

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5 274 The level of COI revealed in this study is greater than that reported in a 2015 survey of
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7 275 Canadian physicians, where 46% said that they had been retained by a pharmaceutical
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9 276 company in some capacity at some point in their career (7). It is also substantially larger than
10
11 277 the level of FCOI of people serving on FDA advisory committees. These are committees
12
13 278 convened by the FDA to vote on whether the FDA should approve new drug applications. An
14
15 279 analysis of 379 meetings held over 15 years by 15 committees found that the median level of
16
17 280 meeting “conflictedness” (percentage of individuals with a reported FCOI) was around 13%
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19 281 (range 2% to 29%). On average, committees reported that half of their meetings were
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21 282 attended by at least 1 person with a financial conflict (6).
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28 284 An additional issue that this study identified was that there is missing information in a
29
30 285 substantial number of FCOI declarations. Statements about stock ownership were not
31
32 286 completed 11.9% of the time and those about a personal or commercial relationship were not
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34 287 completed 12.6% of the time. These omissions raise the question about whether these
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36 288 declarations are just pro forma, i.e., a piece of paper to be filled out and then ignored by the
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38 289 pCODR. Moreover, there is evidence that declarations about FCOI are often omitted in
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40 290 medical journal articles (8, 9), in clinical practice guidelines (10, 11) and among people
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42 291 presenting at conferences (12).
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49 293 Two important questions are whether the conflicts held by the clinicians influenced their
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51 294 view about the drug-indication being considered and whether the conflicts influenced the
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53 295 final decision by the pCODR. pCODR does not publish the submissions from the clinicians
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55 296 but summarizes them in its reports and does not necessarily attribute views to individual
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57 297 people or individual groups in the case where more than one individual or group makes a
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3 298 submission. Therefore, when there are submissions from more than one individual clinician
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5 299 or more than one group of clinicians it is generally not possible to link views about a drug-
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7 300 indication (positive, neutral, negative) to the FCOIs. However, 75% of the time when the
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9 301 preliminary recommendation of the pCODR was not to fund the drug clinicians making
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11 302 submissions disagreed with the decision and most of the clinicians who disagreed with the
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13 303 recommendation declared a FCOI with the company making the product. These finding
14
15 304 suggest that FCOI did determine clinicians' views about the product. This suggestion needs
16
17 305 to be tempered by a couple of points. First, clinicians may have held favourable views about
18
19 306 the drug-indication before their relationship with a drug company started. Second, there can
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21 307 be a legitimate argument about whose views of the drug-indication were more accurate, those
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23 308 of the clinicians or those of the pCODR.
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31 310 As to whether or not the clinicians had an influence on the final recommendation of the
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33 311 pCODR, it may be relevant that the pCODR only changed its recommendation from do not
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35 312 fund to fund with conditions in one out of the 9 cases where the clinicians disagreed with the
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37 313 preliminary decision. Removing all of the FDA advisory committee members with conflicts
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39 314 would have produced margins less favourable to the drug being considered in the majority of
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41 315 meetings, but this would not have changed whether the majority favoured or opposed the
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43 316 drug (13).
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49 318 In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) serves somewhat the
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51 319 same role as the pCODR (14). In making submissions to the PBAC, companies are able to
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53 320 recruit experts to provide an opinion about their drug and the sponsors have to provide a
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55 321 signed statement from each expert about their FCOIs (15). However, the FCOI documents
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3 322 from these experts are not publicly available so their degree of FCOI cannot be compared to
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5 323 that of experts giving input to pCODR.
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10 325 The literature about whether disclosure of FCOI affects trust in individual doctors, the
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12 326 pharmaceutical industry and the healthcare system in general is mixed. A systematic review
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14 327 about the impact of disclosing financial ties in research and clinical care, found that patients
15
16 328 believe that these influenced professional behaviour, decreased the quality of research
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18 329 evidence and should be disclosed (16). More recently, one study reported that when patients
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20 330 believed that a gift relationship existed, they had lower levels of physician trust and higher
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22 331 rates of health care system distrust (17). While the level of payments affected perceptions of
23
24 332 honesty and fidelity in individual physicians, viewing an online disclosure database did not
25
26 333 affect patients' trust ratings for the medical profession or the pharmaceutical industry (18).
27
28 334 Patient attitudes about FCOI in cancer research seems to be more forgiving. Most patients in
29
30 335 cancer-research trials were not worried about FCOI between researchers and drug companies
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32 336 and would still have enrolled in the trial if they had known about these relationships (19). The
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34 337 only Canadian study on patients' attitudes found that public opinions on physician–
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36 338 pharmaceutical industry interactions differ depending on the scenario but suggested a
37
38 339 significant level of concern regarding interactions involving direct financial benefit to
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40 340 physicians (20). Whether the conflicts held by clinicians leads to a public perception that the
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42 341 pCODR process is biased is a question that this current study cannot answer but should be the
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44 342 subject of further research.
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53 344 *Limitations*

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56 345 These results about the presence of conflicts only apply to clinicians making voluntary,
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58 346 unsolicited submissions about funding oncology drugs and the distribution of conflicts among
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3 347 other clinicians treating cancer who did not make a submission may be different. Similarly,
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5 348 the results may not apply to clinicians treating other diseases. Clinicians did not comment on
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7 349 9 out of 46 preliminary recommendations. Whether they agreed with the final
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9 350 recommendation from pCODR is not known although it seems unlikely that they would have
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11 351 changed their views between the preliminary and final recommendations. FCOI declarations
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13 352 were not independently checked to see if there were undisclosed FCOI. The main strength of
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15 353 this study is that it looked at the entire population of recommendations from pCODR where
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17 354 clinicians made a submission about the drug-indication being considered.
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24 356 **Conclusion**

25
26 357 Conflicts with pharmaceutical companies are widespread among experts making submissions
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28 358 to the pCODR. Information about how much experts are reimbursed for the activities that
29
30 359 they undertake on behalf of companies is not disclosed by pCODR and attributing views to
31
32 360 individual clinicians or groups of clinicians cannot be done since only summaries of the
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34 361 submissions are published. pCODR should publish full submissions, the exact amounts that
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36 362 clinicians receive and the names of companies making each of the payments, in order to help
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38 363 determine any association between payments and clinicians' views. pCODR could also
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40 364 consider specifically asking clinicians without any FCOI to make submissions.
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3 **367 References**
4

- 5 368 1. CADTH. About the pan-Canadian Oncology Drug Review (pCODR): CADTH; 2019
6
7 [Available from: <https://www.cadth.ca/pcodr/about-pcodr>.
8 369
9
10 370 2. pCODR expert review committee terms of reference: CADTH; 2016 [updated May.
11
12 Available from:
13
14 [https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Co](https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_expertreviewcommittee.pdf)
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16 [mmittee%20%28pERC%29/pcodr_expertreviewcom](https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_expertreviewcommittee.pdf)
17 373 [_tor.pdf](https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_expertreviewcommittee.pdf).
18
19 374 3. CADTH Common Drug Review. Procedure for the CADTH Common Drug Review:
20
21 CADTH; 2014 [updated August. Available from:
22 375
23 https://www.cadth.ca/sites/default/files/cdr/process/Procedure_for_CADTH_CDR.pdf.
24 376
25
26 377 4. CADTH. pCODR clinician input and feedback: CADTH; 2019 [Available from:
27
28 <https://cadth.ca/pcodr/clinician-input-and-feedback>.
29 378
30
31 379 5. CADTH. Frequently asked questions: clinician input and feedback for the CADTH
32
33 pCODR program: CADTH; no date [Available from:
34
35 <https://cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pCO>
36 381
37 [DR_ClinicianInputFeedbackFAQ.pdf](https://cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pCODR_ClinicianInputFeedbackFAQ.pdf).
38 382
39
40 383 6. Pham-Kanter G. Revisiting financial conflicts of interest in FDA advisory
41
42 committees. *Milbank Quarterly*. 2014;92:446-70.
43 384
44
45 385 7. Leslie C. Relationship between MDs and pharma changing. *The Medical Post*. 2015
46
47 September 15.
48 386
49 387 8. Weinfurt K, Seils D, Tzeng J, Lin L, Schulman K, Califf R. Consistency of financial
50
51 interest disclosures in the biomedical literature: the case of coronary stents. *PLoS One*.
52 388
53 2008;3:e2129.
54 389
55
56
57
58
59
60

- 1
2
3 390 9. Rasmussen K, Schroll J, Gøtzsche P, Lundh A. Under-reporting of conflicts of
4
5 391 interest among trialists: a cross-sectional study. *Journal of the Royal Society of Medicine*.
6
7 392 2015;108:101-7.
8
9
10 393 10. Moynihan R, LAI A, Jarvis H, Duggan G, Goodrick S, Beller E, et al. Undisclosed
11
12 394 financial ties between guideline writers and pharmaceutical companies: a cross-sectional
13
14 395 study across 10 disease categories. *BMJ Open*. 2019;9:e025864.
15
16
17 396 11. Khan R, Scaffidi M, Rumman A, Grindal A, Plener I, Grover S. Prevalence of
18
19 397 financial conflicts of interest among authors of clinical guidelines related to high-revenue
20
21 398 medications. *JAMA Internal Medicine*. 2018;178:1712-5.
22
23
24 399 12. Choo K, Yi P, Burns R, MoHan R, Wong K. Variable reporting by authors presenting
25
26 400 arthroplasty research at multiple annual conferences. *The Journal of Arthroplasty*.
27
28 401 2017;32:315-9.
29
30
31 402 13. Lurie P, Almeida C, Stine N, Stine A, Wolfe S. Financial conflict of interest
32
33 403 disclosure and voting patterns at Food and Drug Administration drug advisory committee
34
35 404 meetings. *JAMA*. 2006;295:1921-8.
36
37
38 405 14. Pharmaceutical Benefits Scheme. Pharmaceutical Benefits Advisory Committee
39
40 406 (PBAC) membership: Australian Government Department of Health; 2019 [Available from:
41
42 407 <http://www.pbs.gov.au/info/industry/listing/participants/pbac>.
43
44
45 408 15. Pharmaceutical Benefits Scheme. Guidelines: Appendix 1 expert opinion: Australian
46
47 409 Government Department of Health; 2019 [Available from:
48
49 410 <https://pbac.pbs.gov.au/appendixes/appendix-1-expert-opinion.html>.
50
51
52 411 16. Licurse A, Barber E, Joffe S, Gross C. The impact of disclosing financial ties in
53
54 412 research and clinical care: a systematic review. *Archives of Internal Medicine*. 2010;170:675-
55
56 413 82.
57
58
59
60

- 1
2
3 414 17. Grande D, Shea J, Armstrong K. Pharmaceutical industry gifts to physicians: patient
4
5 415 beliefs and trust in physicians and the health care system. *Journal of General Internal*
6
7 416 *Medicine*. 2011;27:274-9.
- 8
9
10 417 18. Hwong A, Sah S, Lehmann L. The effects of public disclosure of industry payments
11
12 418 to physicians on patient trust: a randomized experiment. *Journal of General Internal*
13
14 419 *Medicine*. 2017;32:1186-92.
- 15
16
17 420 19. Hampson L, Agrawal M, Joffe S, Gross C, Verter J, Emanuel E. Patients' views on
18
19 421 financial conflicts of interest in cancer research trials. *New England Journal of Medicine*.
20
21 422 2006;355:2330-7.
- 22
23
24 423 20. Holbrook A, Lexchin J, Pullenayegum E, Campbell C, Marlow B, Troyan S, et al.
25
26 424 What do Canadians think about physician-pharmaceutical industry interactions? *Health*
27
28 425 *Policy*. 2013;112:255-63.

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31 426
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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	5	2 (40)	2 (40)
ozogamicin			
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.

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3 **Supplementary File 2: Number of times conflict with company mentioned**
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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-11
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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 (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	10-12
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.