Article details: 2016-0085	
Title	Evaluating alignment between Canadian Common Drug Review recommendations and provincial health technology assessment decisions: an exploratory study
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Reviewer 1	Dr. Joel Lexchin
Institution	York University, School of Health Policy and Management, Toronto, Ont.
General comments (author response in bold)	Methodologic issues Were the comparisons between the CDR decisions and provincial listing done by one person or more than one? **We thank reviewer 1 for this question and have included the following text to clarify how the comparisons were conducted: 'The HTA recommendations and provincial listing decisions were collected by a single researcher to ensure consistency.' (page 5, paragraph)** How was the semi-structured interview developed and was it pilot tested? **We thank the reviewer for raising this question regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** How was information extracted from the interviews and was it done by more than one person? Was software used to analyze the interviews? **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Other issues The abstract only provides results and discussion from the first of the studies. **We agree that the abstract only provides results for the first study and understand why the reviewer has raised this question for the manuscript. However, this is now aligned with the manuscript as the second study has been removed.** What was the rational for choosing participating plans just from Alberta, British Columbia and Ontario? **We thank the reviewer for asking this clarification question and additional information has now been added to the methods section:** **'We used information from the public domain to identify the key agencies involved in the regulatory, HTA and reimbursement process for the CDR and Alberta, British Columbia, Ontario and Quebec [12-16]. Alberta, British Columbia and Ontario were chosen for review as these are the three most populous provinces with public payers that participate in the CDR. Quebec was included as it is the only province that does not participate in the CDR and reviews medicines independently.' (page 5, paragraph)** At the start of the Discussion the authors say that the provinces are increasingly aligned with CDR recommendations but they don't provide any comparisons with previous studies until later on in the Discussion. Furthermore, the authors need to discuss if there are any methodologic differences between their study and the previous ones that they are using for comparison purposes. **We thank the reviewer for raising the issue of the comparative studies and have reordered the discussion to discuss the comparative studies first. Furthermore, we have now outlined methodological differences between our study and other studies in the text:** **'Gamble et al. [8] calculated agreement between the Common Drug Review and 11 public drug plans for all Common Drug Review recommendations issued from inception to May 2009 using the binomial categories 'listed' and 'not listed'. The comparison of the percentage agreements and kappa coefficients that were calculated for this study also used binomial classifications and a comparison of study results suggests that provincial payers are now more aligned with Common Drug Review recommendations.' (page 10, paragraph)** **'Unlike this study, Anis et al [22] directly compared provincial pairs as there was no CDR at the time of the study and produced kappa coefficients ranging from k=0.06 to k=0.39 for the Alberta, British Columbia, Ontario and Quebec. This study calculated kappa coefficients for these four provinces compared with recommendations from the Common Drug Review and results ranged**

	from k=0.432 to k=0.663.' (page 11, paragraph) **'The results from MacDonald and Potvin (2004) are more difficult to compare as they used 'full' and 'restricted' as the two categories for comparison, unlike this study which used positive and negative listing recommendations [23]. Morgan et al. also used different reimbursement categories and did not limit their comparison only to new medicines issued a reimbursement recommendation from the Common Drug Review [24]. The results of this study are also difficult to compare with Attaran et al. [7], which only considered the first 25 and last 25 drug reviews published on the Common Drug Review in February 2009. Attaran et al. [7] also calculated percentage agreements using a multinomial classification category which have been criticised due to the difficulty of accurately comparing restrictions [25]. The binomial categories used in this study, Anis et al. [22] and Gamble et al. [8] provide mutually exclusive categories for comparison, but it is also argued that these can also be too simplistic. Therefore, this study used both multinomial and binomial classifications for comparison.' (pages 11- 12, paragraph)** The value of having patient input is not discussed in the Interpretation section. Having asked people working in plans about this issue the authors should discuss the results. **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** The authors need to go into more depth in discussing how the CDR model could be applied in Europe, e.g., they need to discuss the difference between the EU-wide decision making of the European Medicines Agency versus the individual national decisions about public funding. **We agree with the reviewer's request that we provide more depth to the discussion for how the CDR model could be applied in Europe and have added additional text in interpretation section and conclusion:** **'This model has the potential to be of value in other regions with multiple payers, such as Europe. Currently, the European Medicines Agency provides centralised marketing authorisation for all member states, but the reimbursement and decision-making processes remain the responsibility of each country and are highly fragmented. The CDR model could be implemented in Europe if a centralised body evaluated new medicines to inform reimbursement recommendations for European payers [2].' (page 9, paragraph)** **'It is envisaged that the outcome of this study could have implications for other regions with a centralised regulatory authority and a fragmented payer environment, such as Europe.' (page 14, paragraph)**
Reviewer 2	Dr. Irfan Dhalla
Institution	University of Toronto, Department of Medicine, Toronto, Ont.
General comments (author response in bold)	Comment 1 (abstract) I am not sure that everyone would agree that kappa of 0.43 or 0.56 is "moderate to strong". Some would say this is just fair agreement. **We thank the reviewer for raising this question and we have amended the classification of the four kappa scores (0.432, 0.560, 0.647, 0.663) to 'moderate to substantial' based on the two following highly cited sources:** **Landis & Koch (1977):** **< 0 Poor agreement** **0.0 – 0.20 Slight agreement** **0.21 – 0.40 Fair agreement** **0.41 – 0.60 Moderate agreement** **0.61 – 0.80 Substantial agreement** **0.81 – 1.00 Almost perfect agreement** **Altman DG (1999)** **< 0.20 Poor** **0.21 – 0.40 Fair** **0.41 – 0.60 Moderate** **0.61 – 0.80 Good** **0.81 – 1.00 Very good** Comment 2 (abstract) Perhaps the results from the second study should be included in the Results section of the abstract? **We agree that the abstract only provides results for the first study and understand why the reviewer has raised this question for the original manuscript. However, this is now aligned with the amended manuscript as the second study has been removed.**

	Comment 3 (abstract) The interpretation mentions "increases in alignment" but I'm not sure if the study looked at whether agreement increased over time? **We thank the reviewer for this observation and have amended the text to clarify that we drew the conclusion that alignment has increased overtime in relation to results from a previous study with a similar methodology and therefore we felt the comparison was justified. To prove this more effectively, this study could be repeated with a more recent cohort of recommendations.** Comment 4 (introduction) I think the definition of HTA at the end of the first paragraph is arguably too narrow. The WHO definition refers to social, organizational and ethical issues, in addition to therapeutic benefits and cost effectiveness. **We thank the reviewer for this comment and the definition of HTA has been expanded in line with the WHO definition to include the social, ethical and organisational impact:** **'HTA is a multidisciplinary field of research that generally considers the therapeutic benefits, cost effectiveness, social, ethical and organisational impact of a new health technology such as a pharmaceutical, medical device, diagnostic or surgical intervention that can be used to inform health policy and reimbursement decisions'(page 3, paragraph)** Comment 5 (introduction) In the second paragraph, it may be worth mentioning that some provinces began HTA work well before the establishment of CCOHTA. **We thank the reviewer for this suggestions and have amended the text to clarify that provinces were working in HTA before CCOHTA was established:** **'Canada has a long history of health technology assessment with the Conseil d'Évaluation des Technologies de la Santé du Québec launched in 1988. The Canadian Coordinating Office of Health Technology Assessment (CCOHTA) was established in 1989, and health technology assessment was also growing at the provincial level in Alberta, British Columbia and Saskatchewan [3-4].' (page 3, paragraph)** Comment 6 (introduction) I am not sure whether "innovative" is the right word in the last sentence of paragraph two? I think the goal is to decrease the time taken for patients to access effective drugs that provide reasonably good value for money? **We agree with the reviewer's comment and 'Innovative' has been changed to 'new':** **'CADTH established the Common Drug Review to standardise the Canadian health technology assessment environment for drug reviews and recommendations, harmonise decision making across different public drug plans, reduce the duplication of work and ultimately to decrease the time taken for patients to access new medicines [5].' (page 3, paragraph)** Comment 7 (introduction) Kudos to the authors for mentioning the criticisms of CADTH on page 5. **We thank the reviewer for this comment.** Comment 8 (methods) I suggest providing more detail to indicate what is meant by 'representatives from the four provinces'. Four provincial governments? HTA producers in academia? Somewhere else? More detail could be provided about the interviews and the participants **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Comment 9 (methods) Also, is this an N of 4? **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Comment 10 (results) I am not sure the "maps" are results per se. These might belong in an appendix, with reference to them in the introduction? **We thank the reviewer for this comment and have now only included the process maps in the appendix.** Comment 11 (results) Although Table 4 provides some useful summary information, I was surprised not see

	the raw data presented in a 2 x 2 table (or m x n table for comparison at multiple levels) for each of CDR vs Ontario, CDR vs Quebec, etc. Without such a table it is very difficult to see where the disagreements lie. **We thank the reviewer for this comment and we have selected a table to present the raw data with proportions of positive and negative recommendations for comparison and included this in the results section.** **Table 2. Proportion of medicine-indication pair recommendations by binomial categories** **HTA agencies and payers Positive recommendation (95% CI) Negative recommendation (95% CI)** **CDR (n=86) 46.5%(n=40)** **(36.3%; 57.0%) 53.5% (n=46)** **(43.0%; 63.7%)** **Alberta (n=76) 52.6% (n=40)** **(41.6%; 63.5%) 47.4% (n=36)** **(36.5%; 58.4%)** **British Columbia (n=84) 56.0% (n=47)** **(45.3%; 66.1%) 44.0% (n=37)** **(33.9%; 54.7%)** **Ontario (n=81) 63.0% (n=51)** **(52.1%; 72.7%) 37.0% (n=30)** **(27.3%; 47.9%)** **Quebec (n=81) 50.6% (n=41)** **(40.0%; 61.2%) 49.4% (n=40)** **(38.8%; 6.0%)** Comment 12 (results) How long were the interviewers? How were the themes identified? **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Comment 13 (interpretation) I am not sure data were presented to support the use of the phrase "increasingly aligning" in the first paragraph. There were no temporal trend data presented. **Please see the response provided for a similar comment previously raised (comment number 3).** Comment 14 (interpretation) 3rd paragraph – it seems strange that the interviewees from Ontario and Quebec said they would not proceed to discuss other factors if there were no "added therapeutic benefit" given that many drugs that have equivalent therapeutic benefit are added to the formulary each year. **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Comment 15 (interpretation) Re: "comments and opinions regarding the CDR were unanimously positive", did the authors specifically ask whether CDR could do anything better? **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Comment 16 (interpretation) In the limitations section, the authors might consider mentioning that interviewing only 4 subjects has several limitations – e.g., maybe they did not achieve saturation? **We appreciate the questions the reviewer has raised regarding the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** Comment 17 (interpretation) Same comments re "moderate to strong" and "increasing alignment" **We thank the reviewer for this observation and please see our responses to comments 1 and 3.** Comment 18 (conclusion figure 1) I can only comment on the Ontario figure, but this seems confusing and potentially inaccurate. For example, does the sponsor deal separately with CADTH and CDR? If not, why are there two arrows? And isn't CDEC inside CADTH, or at least closely affiliated with it as a pan-Canadian committee? Also, I believe Ontario considers patient input

	separately, but I'm not sure about this. **We thank the reviewer for this observation and have now moved the process maps to an appendix as suggested in comment 10. The process map methodology was developed to compare key similarities and differences between national systems, but we have now applied this methodology to compare regional systems.** **The numbered arrows are supposed to indicate key points of information flow (dossier submission and sponsor comments) and we have shown CDEC as a separate advisory body as it is an independent advisory committee for the CDR.** Comment 19 (table 4) See comments above **We thank the reviewer for this further observation and we have now added the table as suggested in comment 11.**
Reviewer 3	Dr. Steven Morgan
Institution	University of British Columbia, Centre for Health Services and Policy Research, Vancouver, BC
General comments (author response in bold)	This paper doesn't acceptable job presenting the findings concerning concordance of formulary listings. The key point that the authors attempt to make in this paper is that the degree of concordance may be improving over time. This may be true, and they present some data to support it; however, the authors assert this conclusion in the interpretation section of the paper before they actually discuss the data to support it. Revisions to better sequence the presentation and discussion of findings appear needed. **We thank the reviewer for this observation and we have now amended the interpretation and discussion accordingly.** The content related to interviews with key informants is underdeveloped. This qualitative component of the study lacks important details concerning goals, methods, data analysis, and validation (eg, triangulation, thematic saturation,...). As presented, the qualitative work appears to risk confirmation bias. **We appreciate that the reviewer has queried the qualitative part of the study. We have now followed the advice of the Editor and removed the qualitative component of the study from the manuscript.** The majority of the process maps concern regulatory stages that are common across jurisdictions. As such, these process maps add relatively little to the paper. I would recommend that they be cut. **We thank the reviewer for this comment, the issue of the process maps was also raised by another reviewer and at the reviewer's request these maps have been removed to the appendix.** Thus, I would recommend editing this to be a clearer, more focused paper on the core point of this research study: that there is a moderate degree of concordance between formulary listings and CDR recommendations. **We agree with the reviewer and have removed the qualitative part of the study** The authors should cite work related to this, which raises important issues with respect to the ease with which formulary decisions will be concordant on some decisions and the difficulty with which it might be reached on other decisions. Relevant papers include, but are not limited to, the following: Menon D, Stafinski T, Stuart G. Access to drugs for cancer - Does where you live matter? Canadian Journal of Public Health 2005;96(6):454-458. Morgan SG, Gillian H, Raymond C, Blais R. Breadth, Depth and Agreement among Provincial Drug Formularies in Canada. Healthcare Policy 2009; 4(4):162-284. For more context of prior work in this area, the authors might also consider reviewing the following papers: Gregoire JP, et al. Inter-provincial variation in government drug formularies. Canadian Journal of Public Health 2001;92(4):307-12. MacDonald K, Potvin K. Interprovincial variation in access to publicly funded pharmaceuticals: A review based on the WHO Anatomical Therapeutic Chemical classification system. Canadian Pharmaceutical Journal 2004;137(7):29-34. **We thank the reviewer for these suggestions and have now included reference to the recommended papers by Morgan et al. and MacDonald and Potvin.** **We limited the scope of this research to only drugs reviewed by the Common Drug Review which excludes oncology products. Therefore, we have not included the suggested paper by Menon et al. titled 'Access to drugs for cancer - Does where you live matter?'.**