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Title	Use of real-world evidence in cancer drug funding decisions in Canada: a qualitative study of stakeholders' perspectives
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Reviewer 1	Christopher Booth
Institution	Department of Oncology, Queen's University, Kingston, Ont.
General comments (author response in bold)	This is a well written and important piece of work. The methods are strong and the findings are relevant for health policy. My only suggestion is that the authors expand on the potential risks of RWE to generate erroneous findings re: effectiveness and the implications of this. This is particularly problematic in settings where there is not RCT evidence showing efficacy. i.e. using RWE to look for effectiveness when a RCT has already shown efficacy is much less "dangerous" than using RWE to replace RCTs. I do not think the authors are suggesting RWE replace RCTs but this concept should be addressed since there is a growing movement (esp in the US) to forego RCTs and simply use RWE. This is a major problem. dangerous" **We now address this point in the discussion:** **"Another concern raised by participants was using RWE to replace RCT data to demonstrate efficacy, given the risk of bias and uncertainty. Participants suggested using conditional reimbursement to manage uncertainty associated with RWE. This is consistent with how European HTA agencies have been found to use RWE, rather than to understand treatment effects or in initial reimbursement decisions.[21]" (Page 15)**
Reviewer 2	Karen Lee
Institution	DCR, Canadian Agency for Drugs & Technologies in Health, Ottawa, Ont.
General comments (author response in bold)	Thank you for the opportunity to review this manuscript. The authors have reported on a survey to understand the views on the potential use of RWE within decision making context in Canada and have appeared to gain some useful insights from various stakeholders. The manuscript would be of more interest to the readership if some of the applications of this work can be discussed further, and perhaps reporting of results in a way to highlight trends and how the authors have reached their recommendations. As it is, the manuscript currently provides more background to what might be a larger project. More details and discussion may make this a stronger standalone piece. The title of the manuscript "How can Real-World Evidence be incorporated into cancer drug funding decisions in Canada? A qualitative study of stakeholders' perspectives" suggests how RWE could be incorporated into cancer drug funding decisions will be described, but the authors do not really get into these details. Instead, the piece reflects more on the second half of the title, the views on RWE by stakeholders. The paper would benefit perhaps from a more extensive description of survey findings which led to the specific recommendations, and analysis as to how this could assist decision makers. For example, authors could further explore some of the responses from different groups of respondents to better understand the different perspectives; it is unclear what was gleaned from the inclusion of international respondents. Perhaps more detailed reporting of survey results would provide more insight to the authors recommendations.

	Thank you for your comment. To clarify, this was a qualitative description study, not a survey, in which we have provided a thematic analysis to describe each theme with supporting quotes to illustrate the challenges, potential solutions, and recommendations described by participants. We have added a section to introduce all qualitative themes before describing each in detail. **"RESULTS** **Participant characteristics** **Forty individuals were invited to participate. Eight did not respond to the invitation email, and two declined to participate. A total of 30 stakeholders (Table 1) participated in interviews (~30-75 minutes long).** **Summary of qualitative themes** **Four themes were identified related to participants' views and experiences with RWE: 1) the value of RWE in cancer drug funding decisions, 2) the need for a cultural shift to adopt RWE in decision-making, 3) Canadian RWD data infrastructure is currently inadequate for decision-making, 4) the need for committed investment in building capacity to collect and analyze RWE, and 5) the need for increased collaboration between key stakeholders. Each theme is described in detail in the following sections." (Page 8)** **In addition, we provided additional illustrative quotes corresponding to each theme in a table in light of the word limit. In these ways, we have tried to report our rich qualitative results of the major discussions and perspectives found in our data, while also adhering to the word limit.** **With regard to the international perspectives, these were added to the study design in attempt to provide wider context to our data. In general, this data was helpful, but did not lead to any major findings beyond what we have reported in the manuscript, especially in light of the length limitations.** The aim of the study ("This study aimed to inform CanREValue framework development through exploring Canadian and international stakeholders' views and experiences with RWE") appears relevant to the project but in terms of dissemination of information to a broader audience needs more discussion/presentation. As mentioned, this work as presented, seems more like a background piece to the larger project. For this to be published on its own, more is needed to highlight challenges, gaps, and needs (infrastructure, methods, knowledge translation, etc) to be able to more broadly understand the implications of the survey to RWE moving forward. For example, was there any comment on the increasing use of single arm studies in oncology? As use of RWE could be more important, or maybe this was less observed in 2018? The issue with RWE is often that it is not experimental in design, and the concern is that using data to illustrate a finding may be less robust than one more experimental in design. Was this raised at all (indirectly) by interviewees? What might support greater use by decisions makers? This would be something might be reported on specifically. **Participants did not specifically comment on the use of single arm RCTs in oncology, and mainly discussed the use of RWE generated from post-market data. Indeed, our interviewees did raise concerns about RWE being less robust than RCT data and proposed conditional reimbursement as a solution to address the uncertainty of RWE, which we report in the Results. Below are excerpts that illustrate these points:** **"While participants were enthusiastic about RWE's external validity over**

	RCTs, they recognized that a cultural shift was required for decision makers to move beyond the traditional, "gold standard" (#11, Canadian) evidence provided by RCTs. In contrast, RWE was perceived as susceptible to bias and confounding, with inconsistent data collection, analysis methods, and conclusions. To adopt RWE in decision-making, decision-makers would need to trust RWE and accept RWE's uncertainty (Table 2, Quote #014). Some participants perceived the incorporation of RWE into decision-making as a potential catalyst for transforming healthcare data collection and use in Canada. These participants recommended developing mechanisms to manage uncertainties through conditional approval, whereby results can continue to be captured until the data have matured to inform the final decision about public funding for a drug." (Page 10) **With respect to highlighting challenges, gaps and needs, our study provides an in-depth, qualitative analysis of the challenges to using RWE (e.g. data quality, lack of cooperation between public and private sector, lack of expertise for RWE analysis), and highlights solutions proposed by our participants (e.g. clarify role of RWE, build infrastructure and capacity to collect and analyze RWE, use conditional reimbursement), which are reported throughout the results and summarized in Table 3. We have also re-structured our Discussion to further highlight key challenges and solutions identified by our participants and from the literature.** **With regard to relevance to a wider context, we agree that this information will provide a valuable background to the larger study. However, we also feel that our data will be helpful to other healthcare systems in Canada and beyond. RWE is increasingly being used in Canada (beyond oncology) and many countries across Europe are exploring the use of RWE to help guide decision making with RWE. In both of these cases, our work will provide valuable insight into what decision-makers and users need to consider when incorporating RWE into their decisions.** The manuscript provides an interest start to the work but more details are required to achieve the title of the manuscript, to provide some tangible ways in which RWE could be effectively incorporate into funding decisions. **Thank you for the comment. We have provided a detailed thematic analysis to describe each theme with supporting quotes to illustrate challenges, potential solutions, and recommendations described by participants. We have added a section to introduce all qualitative themes before describing each in detail (as described above, on page 8 of our manuscript). We would welcome the opportunity to present our qualitative data in more detail, and thus we have provided additional illustrative quotes corresponding to each theme in a table in light of the word limit. In these ways, we have tried to report our rich qualitative results of the major discussions and perspectives found in our data, while also adhering to the word limit.** Areas for clarification: - Page 6 (of 34)/line 17-22 – true but I might suggest that the clinical data is key. As outcomes are predicted within economic models but there is no clinical data to validate/refute predictions **Thank you for your comment. We are unsure what exactly is being referred**

	to here, but we agree that clinical data is key, which is congruent with our qualitative findings. **"RWE was described as a valuable supplement to inform post-market decisions about continued funding, price re-negotiations, or de-listing drugs currently on the formulary. Participants described how RWE could provide post-market clinical data to reduce uncertainty about a drug's long-term performance and assist the payer in price negotiations (Table 2, Quote #002)." (Page 7)** - Page 6/line 51 – how are the objectives of this research relevant to the CMAJ readership? **RWE is increasingly used in decision making for oncology and other spheres of healthcare. There are many opportunities and challenges associated with use of RWE, which are discussed in this manuscript. This is relevant to the CMAJ Open readership of Canadian healthcare providers, policymakers and researchers who may increasingly encounter RWE in their work.** - Page 7/line 47 – were international responses analysed separately? **Each transcript was coded individually, consistent with qualitative methods, and we compared Canadian and international perspectives, as we describe in the methods.** **"Barriers and facilitators to RWE uptake described by Canadian stakeholders were compared to international experts' experiences implementing RWE, to triangulate Canadian perspectives with experiences from other health systems." (Page 8)** - Page 9/line 43 – as the interview was continuously adapted did interviewers go back to initial interviewees? **It is standard practice in qualitative methodology for the interview guide to be adapted based on ideas or themes that are brought up by each of the participants as the interviews are conducted and as themes are identified through the concurrent analysis. The aim of semi-structured, qualitative interviews is not to generate identical data points from each participant, as in a survey, but to explore each participant's views and experiences. Because of the semi-structured nature of the interviews, it is expected that there will be some variation between each interview in terms of what is discussed. It is not standard qualitative practice to re-interview participants as the interview guide is modified. Thus, we did not re-interview participants who had been previously interviewed as we adapted the interview guide.** - Page 11/line 6 – RCT remains gold standard for regulatory and perhaps initial reimbursement decisions but from a reassessment perspective is a validation RCT still considered gold standard? **This is a good question. In terms of our data and our interviews with participants RCT were discussed in a general manner and participants did not explicitly explore the use in RCT at different points in the cycle of funding decision making. Participants largely focused on the certainty that the RCT study design can give them when making decisions about whether to fund a drug – independent of the when the drug is being assessed. To**

	that, they used the RCT in general as a contrast to the uncertainty they felt that RWE might instill in decision makers. Here is an excerpt to illustrate this point: **"While participants were enthusiastic about RWE's external validity over RCTs, they recognized that a cultural shift was required for decision makers to move beyond the traditional, "gold standard" (#11, Canadian) evidence provided by RCTs. In contrast, RWE was perceived as susceptible to bias and confounding, with inconsistent data collection, analysis methods, and conclusions. To adopt RWE in decision-making, decision-makers would need to trust RWE and accept RWE's uncertainty (Table 2, Quote #014). Overall, participants recommended a culture shift away from sole reliance on RCT data." (Page 10)**