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ORIGINAL RESEARCH

Development of a Canadian Guidance for reporting real-world evidence for regulatory and health-technology assessment (HTA) decision-making

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Abstract

Background and Objective: Real-world evidence (RWE) can complement and fill knowledge gaps from randomized controlled trials to assist in health-technology assessment (HTA) for regulatory decision-making. However, the generation of RWE is an intricate process with many sequential decision points, and different methods and approaches may impact the quality and reliability of evidence. Standardization and transparency in reporting these decisions is imperative to appraise RWE and incorporate it into HTA decision-making. A partnership between Canadian health system stakeholders, namely, Health Canada and Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health), was established to develop guidance for the standardization of reporting of RWE for regulatory and HTA decision-making in Canada.

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Study Design and Setting: A collaborative initiative to create structured guidance for RWE reporting in the context of regulatory and HTA decision-making.

Results: The developed guidance aims to standardize and ensure transparent reporting of RWE to improve its reliability and usefulness in regulatory and HTA processes.

Conclusion: This guidance can be adapted for other jurisdictions and will have future extensions to incorporate emerging issues with RWE and HTA decision-making.

Keywords: Observational studies; Real-world evidence; Pharmacoepidemiology; Health-technology assessment; Regulators; Guidelines; Publishing standards; Epidemiologic research design

1. Background

Randomized controlled trials (RCTs) are the gold standard for determining the safety and efficacy of medical products and health technologies, playing a pivotal role in global regulatory and health-technology assessment (HTA) appraisal, recommendations, and decisions [1−5] However, sometimes RCTs cannot be conducted due to trial length, recruitment, cost, and, less commonly, ethical considerations [6], which can impede their widespread use and leave gaps in knowledge for evidence-based regulatory and HTA decision-making. Real-world data (RWD) are an important source to potentially fill such gaps and complement evidence from RCTs. RWD relate to the delivery of health care collected from a variety of sources, like registries, medical records, and administrative databases. Real-world evidence (RWE) is the evidence derived from RWD on the usage and potential benefits or risks of a medical product, including from observational studies or pragmatic trials that leverage RWD [7]. RWE is often more generalizable than evidence from RCTs [8], because RWD is often generated through routine clinical practice. RWE also can provide information on understudied populations who are often excluded from RCTs, such as children, elderly, patients with diverse racial and ethnic backgrounds, and people with a high burden of comorbidities [9]. RWE is also frequently used when the comparator in an RCT is not considered the most relevant standard-of-care comparator in certain jurisdictions. Therefore, RWE can provide valuable insight into the use of health technologies and their effects on clinical outcomes across a multitude of demographics, as well as give insight regarding costs and resource use in a healthcare system. Supplementing RCTs with RWE can help to improve robustness and adaptability of health technology evaluation frameworks [10].

The limitations of RWE include the potential for bias and confounding due to the generation of RWD from routine interactions with the healthcare system. Generation of RWE from RWD is also an intricate process with many sequential decision points, beginning with the study proposal and data acquisition to final statistical analyses and interpretation; different methods and approaches may impact the quality and reliability of evidence. Transparency in reporting these decisions is imperative to appraise RWE. Therefore, there is a crucial need to standardize the development, reporting, and utilization of RWE to harness its full potential to credibly inform evidence-based decision-making in healthcare.

In recognition of this need to standardize reporting of RWE, a partnership between Canadian health system stakeholders, namely Health Canada and Canada's Drug Agency (CDA, formerly known as the Canadian Agency for Drugs and Technologies in Health, or CADTH) was established to facilitate robust regulatory and HTA decision-making processes involving RWE. This partnership aimed to jointly develop a Canadian RWE reporting guidance to promote transparency and limit ambiguity in submissions that include RWE in order to evaluate the suitability of studies for HTA decision-making, while acknowledging the challenges, heterogeneity in uses, and evolving global context of RWE [11] In this article, we describe the methods and development of this national Canadian guidance, entitled *Guidance for Reporting Real-World Evidence*, currently available on the CDA website [11], for reporting RWE for regulatory and HTA decision-making in Canada.

2. Methods

The methods within this paper are limited to the methodology used to develop the *Guidance for Reporting Real-World Evidence*, rather than any methods to conduct or appraise RWE. In alignment with transparent and complete reporting, the Accurant Consensus Reporting Document (ACCORD) checklist can be found in Appendix 1. Figure presents an overview of the process of developing the guidance document.

2.1. Overview and team

To maximize effectiveness of the guidance, align with established global quality standards, and enhance applicability for a broad range of user requirements, the guidance was developed through a three-phase process that identified, extracted, and refined items related to RWE study components and reporting from existing documents. Phase 1 leveraged two existing environmental scans related to use

What is new?

Key findings

- Describe the methods to develop the Guidance for Reporting Real-World Evidence and checklist for reporting real-world evidence (RWE) for regulatory and health-technology assessment (HTA) decision- making in Canada.

What this adds to what was known?

- Establishing standardization and transparency to reporting of RWE that is used in decision- making in Canada.

What is the implication and what should change now?

The establishment of this guidance is foundational to implementing high-quality RWE into decision making for regulatory and HTA decisions and can be adapted to other juris.

of RWD and RWE [12,13] and an evidence-mapping process to extract candidate recommendations on reporting and methodological considerations to be included in the guidance. Phase 2 used a two-round, modified Delphi process with an expert methods panel to select final recommendations from the candidate list, along with additional relevant items if required. This phase also incorporated considerations for operationalizing the recommendations as well as special considerations for the Canadian context. Phase 3 implemented a stakeholder consultation plan and methods expert panel survey to incorporate and finalize revisions to the guidance based on public and stakeholder feedback.

This 3-phase process was led by three authors (TA, KH, and MT) with experience in pharmacoepidemiology, systematic reviews, and evidence synthesis, henceforth referred to as the ''methods authorship team.'' These authors led the data collection and synthesis for phase 1, attended the consensus meetings as observers (but were excluded from voting in the consensus surveys), and iteratively drafted the resulting guidance document. The consensus process and group discussions were facilitated by a team member (CF) with expertise in Delphi methodology and knowledge translation.

2.2. Phase 1, part I: identification of documents on RWE

Potential articles related to Canadian and international agency guidance, reporting tools, and policy statements on RWD and RWE were first identified through review of two existing environmental scans that identified global documents related to RWD and RWE: a state of knowledge report by the Institut national d'excellence en santé et en services sociaux (INESSS) [12] and a 2020 environmental scan by CDA, *Use of Real-World Evidence in Single-Drug Assessments* [13]. Detailed methods used in these environmental scans are described in the original documents [11] Briefly, authors of the CDA environmental scan conducted a literature search to identify relevant guidelines or policy papers from government agencies through searching of standard databases (OVID MEDLINE, PubMed) and HTA or regulatory agencies websites. A supplemental survey was then sent to a subset of agencies hosting drug review programs to identify additional documents. Similarly, the report published by INESSS conducted a literature search of standard databases and sources of gray

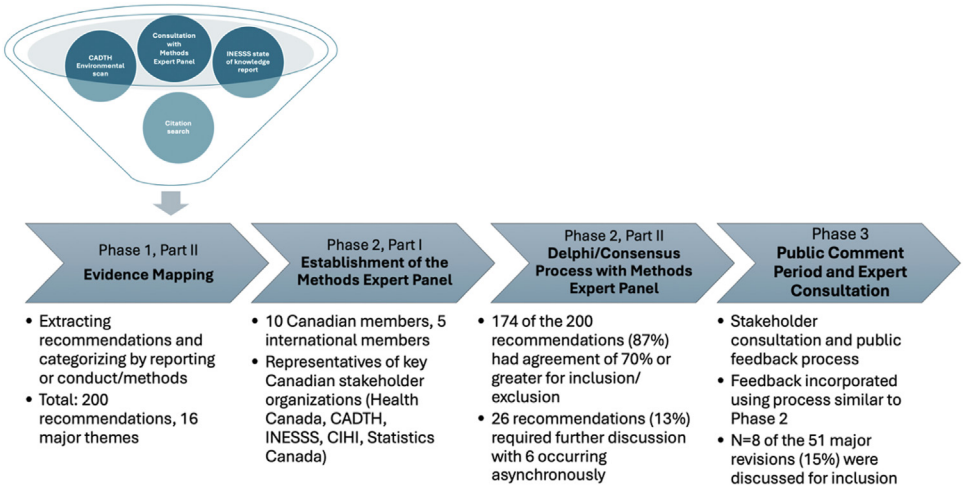

Figure 1. Overview of Method's process to developing Guidance for real-world evidence (RWE).

literature to identify relevant documents. A review of the references and keywords of identified documents was then conducted to identify additional candidate documents.

Next, these environmental scans were extended to identify potential additional documents to review. First, a citation search was implemented on those identified articles cited in reviewed documents that had not yet been identified. Thereafter, the expert methods panel was consulted to identify any additional documents currently in development or not identified by our study team. In total, 37 documents were identified for review and data extraction [9,12,14−48].

2.3. Phase 1, part II: extracting candidate recommendations for RWD and RWE from identified documents (evidence mapping)

Two data extraction tools were created to organize identified candidate recommendations. Recommendations were categorized based on whether they were related to 1) RWD or RWE reporting or 2) RWE study components and methods (Table 1). For each category, we further subcategorized candidate recommendations in other groups (eg, protocol, exposures). Additional subcategories were added if one was identified during the data extraction process. Two team members (KH and TA) independently reviewed all identified documents and independently extracted data on candidate items. A third investigator (MT) reviewed the extracted data for accuracy.

One investigator (MT) removed duplicate recommendations and revised all recommendations with common language (eg, use term "exposure" instead of "drug,'' ''treatment,'' or "intervention"). The other two investigators (KH and TA) then independently reviewed the duplicate removal and standardization of language to confirm accuracy and provide consensus on standardized language. All three investigators then grouped recommendations to major themes (eg, select relevant subcategories were condensed to ''research questions and study design'') to enhance clarity for the methods expert panel. In total, 200 final candidate recommendations were extracted, distilled, and mapped to 16 major themes (Table 2).

2.4. Phase 2, part I: establishment of the methods expert panel authorship and leadership review teams

The methods expert panel was purposefully selected to include ten members based in Canada and five international members. All 15 members were invited and accepted to be part of the methods expert panel. Members were selected based on established expertise in the field, evidenced by a publication record of study design, and/or methods development for RWE. The selection deliberately aimed for diversity in expertise, geographic location, use of diverse data sources (ie, administrative claims and registry), methods expertize (eg, epidemiology, biostatistics, and economics), sex or gender, and career level. International experts were also selected based on experience supporting or leading international RWE guidance. Canadian members of the panel all had a primary affiliation with a Canadian university; for international members, two were affiliated primarily with universities, one was affiliated the US Food & Drug Administration, and two were affiliated with the National Institute for Health and Care Excellence. Detailed information on the stakeholder panel is available in the guidance document online [11]. All experts had to declare potential conflicts of interest and align with the CDA conflict of interest policy [49].

The methods expert panel also included representatives of key Canadian stakeholder organizations (Health Canada, CDA, INESSS, Canadian Institute for Health Information (CIHI), Statistics Canada), who had established expertise in RWE (referred to as the ''leadership review team''). While these panel members did not complete the consensus survey, they participated in all expert methods panel meetings as part of the consensus process. Two CDA representatives (the Vice-President of Scientific Advice, Methodologies, and Resources and Co-Chair of the Guidance for Reporting Real-World Evidence Working Group) as well as the writing team (KH and TA) also attended the meetings as observers.

2.5. Phase 2, part II: delphi/consensus process −structure of modified Delphi and data collection

We then conducted a two-round Delphi process to select recommendations. The 200 recommendations grouped into 16 themes were programmed into an online questionnaire using SurveyMonkey. Each member of the methods expert panel received the list of all 200 recommendations and was asked to determine the importance of including each as an item in the guidance document. Each item was ranked on an anchored scale of 1−4, where ''1'' indicated ''*not important*'' and ''4'' *indicated ''very important*'' for inclusion. Participants had the opportunity to include feedback, discussion points, or clarifications for each item via an open-ended text box. The survey was piloted by 3−4 members internally before being circulated. After being piloted, the survey was circulated by email and participants were given 10 days for independent completion. After survey completion, all items with a score of 1 or 2 were grouped as ''exclude'' and those with a 3 or 4 were grouped as ''include.'' Items that generated 70% or greater agreement to include from respondents were included in the guidance document. The same level of agreement was used for items to exclude. These items were discussed in a virtual meeting that took place on June 22, 2022.

Items that generated less than 70% agreement on whether to include or exclude in the guidance were evaluated in a facilitated discussion (guided by CF). For each item, participants voted on whether to ''*include,*'' ''*omit,*'' or ''*revise*'' each item using an online polling feature. Items

Table 1. Data extraction categories and subcategories for candidate recommendations

Category	Subcategories
Reporting of the use of real-world data (RWD) in real-world evidence (RWE)	Study design, setting, participants, study size, variables and definitions, data sources ormanagement, reporting on follow-up time, data access and cleaning methods, data linkage, bias, statistical methods, adverse event reporting, deviations from protocol, data transformations, governance, statistical software, participant consent, minimum dataset requirements, quality assurance, data security, data codes, reporting on participants, descriptive data, outcome data, main results, other analyses, limitations, interpretation, generalizability, reliability, presentation of results, and financing
RWE study components	Data quality, data appropriateness or quality or fitness of use, generalizability, data cleaning or dataset creation, study team, protocols or registry or study planning, publication bias, study question or objective or appropriateness, study design, study population, exposure or exposure definitions, controls orcomparators, outcomes, exposure-outcome risk window and follow-up, causality or confounders or bias or sensitivity analyses, effect modifiers and subgroup effects, missing data, analysis, interpretation and dissemination of results, other notes, and other documents cited

that generated 70% or greater consensus were included, omitted, or revised, as per group consensus. Participants voted on each of the items (to include or exclude) and were requested to provide comments to support their decisions within 14 days. Additionally, participants took part in a general discussion about the scope, content, and style of the guidance document while maintaining anonymity. All facilitated discussions were recorded, transcriptions were generated, and the methods authorship team wrote detailed notes.

Following the first discussion, the methods authorship team drafted the first iteration of the guidance document. Items determined to be included by the methods expert panel were listed in a reporting checklist. This checklist was accompanied by a narrative document that provided further guidance on how to interpret and implement the items in RWE submissions. The guidance document was then circulated to the methods expert panel for review and feedback. Additional feedback was collected from internal stakeholders from CDA and Health Canada. The authorship team (TA, KH, and MT) compiled the feedback and a second facilitated discussion (guided by CF) on September 20, 2022. The discussion was conducted to determine which feedback should be incorporated and which items should be revised. An online polling feature to 'include' or 'not include' feedback was available as applicable when consensus was not reached via discussion. Finally, members had in-depth discussions to define scope, content, and style of this document. Discussion points and asynchronous detailed feedback were also collected via email and incorporated into the guidance document as appropriate by the methods authorship team, resulting in an updated draft of the guidance document.

2.6. Phase 3: stakeholder consultation and guidance revisions

A stakeholder consultation and public feedback process was implemented to engage with members of the Canadian health-technology ecosystem. A draft of the guidance document was posted on the CDA website for public and stakeholder review and feedback for 8 weeks. During this stakeholder feedback period, members of the methods authorship team and leadership review team participated in multiple in-person and virtual events and leveraged established networks to increase visibility of the posted draft report for comment and to offer opportunities to provide additional feedback.

The methods authorship team and leadership review team collaboratively reviewed the feedback and grouped comments into general themes that could be applied throughout the document (eg, consistency of language) or RWD or RWE reporting-specific feedback. Major revisions to the document based on feedback specific to RWD or RWE reporting were grouped by theme and presented to voting members of the methods expert panel in a survey similar to that used in phase 2, wherein they could include or exclude a revision and could provide additional comments. Major revisions were defined as any revisions that substantially altered the meaning or content of the text. Changes such as rewording a sentence for clarity, adding examples, adding extra citations, changing a figure or table caption, or adjusting the formatting of the manuscript were considered minor. A revision was included or excluded if there was 70% or greater agreement from the methods expert panel on the survey item. A virtual meeting with the methods expert panel was held in a similar fashion to the meetings in phase 2, whereby individuals participated in a facilitated discussion (guided by CF) of each item that did not generate consensus. Revisions that generated 70% or greater agreement were included in or excluded from the guidance document accordingly.

3. Results

A total of 13 respondents from the methods expert panel completed the initial survey to include or exclude candidate

Table 2. Results from first methods expert panel consensus survey on candidate recommendations related to real-world evidence reporting and study components

Theme	Number of items	Number of items with >70% agreement[a] (%)	Number of items to Be excluded
1. Study design and question	22	18 (82%)	2
2. Setting and context	11	9 (82%)	0
3. Data access and cleaning methods	14	8 (57%)	1
4. Data linkage	8	6 (75%)	2
5. Data sources or measurement	12	8 (67%)	0
6. Participants	22	22 (100%)	0
7. Exposure definitions and comparators	12	12 (100%)	0
8. Outcomes	18	12 (67%)	2
9. Variables (covariates and all variable measurement)	9	4 (44%)	0
10. Effect modifiers	3	3 (100%)	0
11. Bias and confounding	8	7 (88%)	2
12. Statistical analysis	19	15 (79%)	0
13. Participant characteristics	9	8 (89%)	0
14. Study findings	12	12 (100%)	0
15. Limitations	9	8 (89%)	0
16. Interpretation and generalizability	12	11 (92%)	2
Total	200	163 (82%)	11

[a] $n = 13$ of $n = 15$ panel members responded.

recommendations (Table 2 provides detailed results.) Most themes had a moderate-to-high proportion of items that generated agreement (67%–92% of items with agreement). Themes with the lowest proportion of items that generated agreement were *variables* and *data access and cleaning methods*. A total of 29 individuals attended the first meeting (14 voting members and 15 stakeholder representatives or observers) to discuss the inclusion or exclusion of 30 candidate items that did not have consensus. Six items were discussed asynchronously after the call due to time constraints.

A total of 14 participants from the methods expert panel and members of the leadership review team from CDA, Health Canada, and INESSS reviewed and provided feedback on the first draft of the *Guidance for Reporting Real-World Evidence* document. Fifteen discussion points based on this feedback were put forward during the second methods expert panel meeting on September 20, 2022, which was attended by 21 participants (10 voting members and 11 observers). After discussion, all discussion points achieved a high level of agreement on whether to include or exclude the respective feedback into the document. Two clarifications regarding the wording of recommendations and language of the aims were further discussed asynchronously via email.

Fifty-four submissions with feedback were received during the consultation and public comment period. Many submissions contained comments and suggested edits from multiple individuals. Pharmaceutical companies, patient groups, and academic institutions comprised more than 50% of groups providing written feedback submissions. Based on the feedback received, a total of 51 major revisions were included in the survey presented to the methods expert panel wherein they voted whether to include or exclude the revision. Eleven of the 14 methods expert panel members completed the survey (note: one expert became ineligible following a change in role). Major revisions to the guidance are listed in the response document published on the CDA website named *Guidance for Reporting Real-World Evidence: Response to Stakeholder Feedback* [50].

All except eight items (eg, inclusion of lab or in vitro evidence, discussing machine learning methods, recommending a specific platform for protocol registration) generated agreement on whether to include or exclude. The remaining eight items were discussed at a virtual meeting on March 1, 2023 with an online polling feature, and all items achieved sufficient agreement after discussion (Appendix 2). The methods expert panel agreed to the addition of a new section in the guidance document concerning communication on how the guidance may be leveraged in practice. The final *Guidance for Reporting Real-World Evidence* [11] document provides a checklist of reporting items to consider (Appendix 3 in the final guidance document), with space to justify why some items may not be included or applicable.

4. Discussion

Through a three-phase process that leveraged established global quality standards and extensive expert and public consultation, we developed the *Guidance for Reporting Real-World Evidence* [11] for RWE related to regulatory and HTA decision-making in Canada. Firstly, this guidance prioritizes and adheres to principles of transparency. Transparency is fundamental to fostering trust in RWE and facilitates RWE quality appraisal to understand its appropriateness for decision-making. Secondly, the guidance document integrates and builds on the existing rigorous frameworks and research in the field and by nature of the methods of its development, aligns with many established best practices globally. Further, by integrating extensive public engagement, it incorporates the perspectives of both Canadian and international experts and end users, enhancing its applicability to Canada while preserving its relevance to other jurisdictions.

This guidance document is intended to support regulators and HTA agencies in establishing reporting standards as they begin to incorporate RWE more formally in appraisals and decision-making. The overall goal of this work is that adherence to the guidelines will better equip stakeholders to assess reliability, quality, and relevance of RWE. Importantly, the *Guidance for Reporting Real-World Evidence* is designed to be flexible and accommodating of the heterogeneous nature of RWE and its rapid evolution, while ensuring that studies are sufficiently detailed and transparent to facilitate regulatory and HTA appraisal and, ultimately, decision-making.

The development of these guidelines marks the initial stride toward formulating high-quality decision-grade RWE that can contribute to regulatory and HTA processes. However, it is crucial to acknowledge that there are still substantial steps that need to be taken to optimize the use of RWE for these purposes. This guidance was intentionally not prescriptive about the exact definition of RWE, when it is appropriate to use RWE or whether to employ specific methods (eg, propensity scores). Next, this guidance was formulated during a period of substantial transformation in the field of RWE. Accordingly, it is expected that this document will undergo periodic updates via iterative processes to adapt to the evolving landscape. In the broader global context, there are also many ongoing initiatives related to RWE quality and reporting, which highlight the vital need for collaborative efforts to ensure alignment of future iterations of the guidance with other documents worldwide, reduce duplicative efforts, and incorporate advancements in RWE.

This first version of the guidance was developed to be broad and methodologically applicable to suit a variety of applications of RWE. However, future work may develop more detailed checklists and quality assessment tools. Further, extensions of this guidance will need to be developed to incorporate emerging tools and challenges, such as the use of prospective data collection, pragmatic trials, artificial intelligence, and rare diseases.

4.1. Limitations

As with many studies and processes, there are some limitations to this work. The methods expert panel included experts across a variety of topics within the field and were recruited to provide diversity in areas of expertize, research, data use, career stage, and geography. The resulting guidance document is therefore informed by these perspectives, along with those of others participating in the public feedback period; however, despite these efforts, it is possible that some perspectives were missed or underrepresented, such as certain patient groups or sectors. Second, the aim was to develop a Canadian-focused guidance to maximize utility to Canadian HTA decision-making. As such, some recommendations contained in the guidance may be less applicable to other countries due to differences in regulatory processes, HTA systems, and data availability. However, because candidate recommendations originated from a host of guidance documents created globally, and international experts were represented in the expert methods panel, the majority of the guidance is likely generalizable to other jurisdictions.

5. Conclusion

Through a rigorous multistep process, CDA, in collaboration with Health Canada, INESSS, and various stakeholders within the Canadian healthcare system, developed the *Guidance for Reporting Real-World Evidence* and accompanying checklist [11] to promote transparency and facilitate appraisal of RWE to support HTA decision-making in Canada. This document outlines the detailed guidance development process providing guiding principles for RWE reporting and study components that align with regulatory and HTA standards, both in Canada and internationally, while incorporating a diverse array of Canadian perspectives. Establishing the guidance is foundational to the implementation of standards for high-quality, decision grade RWE to successfully integrate RWE into the scientific landscape and ultimately improve regulatory and HTA decision-making.

CRediT authorship contribution statement

Mina Tadrous: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Theresa Aves:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis. **Christine Fahim:** Writing –

review & editing, Methodology, Investigation, Formal analysis. **Jessica Riad:** Writing − review & editing, Writing − original draft. **Nicole Mittmann:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Daniel Prieto-Alhambra:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Donna R. Rivera:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Kelvin Chan:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Lisa M. Lix:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Seamus Kent:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Dalia Dawoud:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Jason Robert Guertin:** Writing − review & editing, Methodology, Investigation, Formal analysis. **James Ted McDonald:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Jeff Round:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Scott Klarenbach:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Sanja Stanojevic:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Mary A. De Vera:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Erin Strumpf:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Robert W. Platt:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Farah Husein:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Laurie Lambert:** Writing − review & editing, Methodology, Investigation, Formal analysis. **Kaleen N. Hayes:** Writing − review & editing, Writing − original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis.

Declaration of competing interest

M. T. received financial support from the Canadian Agency for Drugs and Technologies in Health. M. T., T. A., and K. N. H. report a relationship with Canadian Agency for Drugs and Technologies in Health that includes consulting or advisory. N. M., L. L., and F. H. are employed with the Canadian Agency for Drugs and Technologies in Health. There are no competing interests for any other author.

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Supplementary data

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