CanREValue
Value-based decisions from Real World Evidence

Developing a framework for incorporating real-world evidence into drug funding decisions

CanREValue Collaboration Policy Working Groups:

Response to Stakeholder Consultation for the Interim Policy Report 2019

1. Introduction and Background

On December 20th, 2019, the Canadian Real-world Evidence for Value in Cancer (CanREValue) Collaboration initiated a public stakeholder consultation regarding the interim reports drafted by the CanREValue Planning and Drug Selection working group (WG) and the CanREValue Reassessment and Uptake WG.

During the stakeholder consultation, the CanREValue Collaboration sought feedback on three questions regarding the preliminary framework (see Appendix 1). Throughout the consultation period, which remained open until January 31st, 2020, we received a total of 21 responses from different stakeholders (Table 1). A detailed list of respondents is provided in Appendix 2.

Table 1: Summary of respondents

Category	**Total Number of Feedback Reports Received (N = 21)**	**% of All Feedback Reports Received**
Academic/Researcher	3	14.3%
Individual Pharmaceutical Company	10	47.6%
Industry-related organization	3	14.3%
Patient Group	4	19.1%
Other	1	4.7%

The CanREValue Collaboration sincerely thanks the respondents for their submitted feedback and recommendations. Along with the Policy WG chairs and members, the CanREValue Collaboration has carefully considered all feedback from the consultation, and where the WGs felt appropriate, have incorporated the feedback into this revised interim report. Details on the feedback, as well as revisions to the interim report, are described throughout this document.

Section 1: Summary of feedback and responses - RWE Planning and Drug Selection Working Group

Some respondents proposed that manufacturer inputs should be included during the horizon scanning phase of the framework (Step 1), given their familiarity with their drug pipelines. In particular, one respondent noted that manufacturers are in a unique position to provide relevant information for horizon scanning as they are aware of the status of ongoing clinical trials or studies being planned to address relevant questions and issues of uncertainty.

> ***Response:*** Presently, manufacturers have the opportunity to provide information on ongoing studies (clinical trials or RWE studies) at both pipeline meetings with provincial drug programs and pre-submission meetings with HTA bodies. The relevant information collected from manufacturers at these checkpoints can be incorporated readily into the CanREValue framework processes. The preliminary framework will be updated to reflect this strategy.

One respondent suggested "***a list of all planned, ongoing and completed RWE projects detailing objectives, methods, sources and timelines, which should be publicly-accessible to all stakeholders".*** Furthermore, they suggested making all RWE results, along with how the drug was selected for reassessment, publicly available.

> ***Response:*** The WG members are committed to transparency throughout the selection and conduct of RWE projects. The WG members agree that providing as much transparency as possible throughout the selection and conduct of RWE projects is essential. The CanREValue Collaboration intends to maintain a list of uncertainties and will ensure studies being undertaken are publicly available (e.g. posting on the CanREValue website). Further, the collaboration will work with stakeholders to incorporate a mechanism in the framework to report decisions made and results from completed projects to the public. The intention of Step 1 is to identify a general list of questions that may be addressed by RWE projects, and Step 2 and Step 3 are intended to prioritize RWE projects that are relevant to public drug funding for future reassessment. The CanREValue Collaboration intends to make lists of potential projects uncertainties publicly available so that researchers who are interested in conducting RWE projects are aware. In addition to providing the process for the selection of RWE projects, the CanREValue Collaboration will work with stakeholders to incorporate a mechanism in the framework to report decisions made and results from the selected RWE projects to the public.

Some respondents commented that the proposed triggers are quite general. One respondent suggested that the triggers might apply to most oncology files and so should be narrowed to provide clear direction on how the projects will be prioritized. Another respondent disagreed

with the inclusion of "value for money" as a trigger given that many HTA recommendations are conditionally positive with a requirement to improve cost-effectiveness. Additionally, they suggested that given pCODR/INESSS do not have access to confidential prices, this trigger may not be appropriate to include.

> ***Response:*** The WG members acknowledge that the proposed triggers are broad, as the intent is to identify a comprehensive list of questions/uncertainties that could be addressed by RWE projects. The steps following topic identification are designed to focus on prioritizing the projects that are feasible and in the public interest. When the Policy Report was originally released, we had not yet developed any specific prioritization processes. Since that time, we have initiated development of specific details for prioritization, and this work is currently ongoing. Moreover, while the WG members acknowledge the limitations raised regarding the "value for money" trigger, overall the members feel that the trigger is valid in measuring for identifying uncertainties. In particular, value for money is a comparative and incremental measure, as compared to other drugs (which also have undisclosed discounts/confidential prices).

Several respondents highlighted a need to include a broad range of stakeholders to "***provide input into the rationale for the need for an RWD plan and also input into the subsequent RWD generation plan".*** One respondent emphasized the importance of including both patients and healthcare professionals to advise the selection of relevant clinical outcomes.

> ***Response:*** At the time the Interim Policy WG Report 2019 was released, the WG members had not yet developed detailed steps on the approach for initiating RWE studies. As part of the framework, future steps will involve developing a plan for the initiation, planning and conduct of each specific RWE project undertaken. It is proposed that the initial RWE plan undergoes consultation with relevant stakeholders to incorporate their inputs into the proposed RWE project.

One respondent highlighted that "***the conduct of RWE studies by the CanREValue collaboration on its own overlooks credible RWE initiatives conducted by other stakeholders in Canada, including the pharmaceutical industry".***

> ***Response:*** The WG members acknowledge that different stakeholders undertake RWE projects and have included this consideration in the development of the framework. By assessing other ongoing or planned studies in the identification process, as well as disseminating questions of interest publicly, other stakeholders will be made aware of the planned RWE initiatives of interest and those already being undertaken. Furthermore, regulatory and HTA bodies are exploring approaches to incorporate RWE into decision-making irrespective of the evidence source[1,2].

Section 2: Summary of feedback and responses - RWE Reassessment and Uptake Working Group

One respondent suggested replacing the "Implementation & Sustainability" quadrant with an ethics quadrant.

> ***Response:*** The WG members understand the importance of ethical considerations in the context of the reassessment process. Ethical considerations and oversight will be embedded throughout the reassessment process, in the same way that ethics and related concepts such as procedural fairness are embedded in health technology assessment processes in Canada. Ethics is a guiding principle of both CADTH and INESSS and it is expected that this standard would extend to any additional assessment pathways[3,4].

Some respondents suggested that consideration be given to removing the "delist" recommendation category as this might threaten access to medications. One proponent suggested considering a scenario analysis approach when considering delisting.

> ***Response:*** The WG members acknowledge the concerns about access raised by the respondents. When a drug undergoes reassessment review, delisting or disinvestment has been considered by the WG as one potential outcome. It is unlikely that a recommendation would be made to delist a drug in the absence of strong evidence against its use. A recommendation to stop funding may be appropriate if a drug proves to be more toxic and/or much less effective than other available treatment options. Thus, a delisting recommendation is intended to be used when a drug does not demonstrate added benefit or demonstrates harm in relation to other available treatment options. A recommendation to delist would be dependent on the specific circumstances, taking account of available treatment options and appropriateness of choice for patients and clinicians. As is the case with initial recommendations, payers would consider this recommendation in the context of the therapeutic space and appropriateness after careful consideration and deliberation.

Some respondents recommended adapting CADTH's existing review processes of reviewing novel treatment for reassessments. This includes "***adapt [ing] CADTH's current process for disseminating initial pERC recommendations for sharing outcomes at each stage of reassessment".***

> ***Response:*** The WG members acknowledge the respondents' recommendations. The WG members want to clarify that the intended reassessment is modeled after the existing HTA process for assessing drug reviews. As the WG members and HTA stakeholders continue to develop the details of the reassessment process, this suggestion to adapt the current CADTH process for assessment will be explored. Similar to the process

suggested by CADTH's consultation, the CanREValue Collaboration's intent is to facilitate synergism between the initial assessment and potential reassessment processes.

One respondent suggested that a reassessment process be harmonized between CADTH and INESSS.

Response: The WG members have forwarded this feedback to the respective organizations for broader consideration.

Several respondents highlighted that a wide range of stakeholders could potentially be impacted by the reassessment process and therefore should be involved. This list of stakeholders includes patients, decision makers (e.g., provincial and territorial payers), HTA Agencies, clinicians, methodologists (e.g. health economists, health service researchers, epidemiologists), and manufacturers. One respondent emphasized that the stakeholders involved should be without conflict of interest.

Response: The WG members agree with the respondents about the importance of including a wide range of stakeholders in the reassessment process. In the Interim Policy Working Group Report 2019, consideration 10 on page 20 emphasizes this point regarding the need to include all the types of stakeholders mentioned in the feedback. The proposed reassessment review process would also include clinicians and methodologists for the interpretation of the RWE. In future iterations of the report, the suggested stakeholders will be explicitly listed, highlighting the range of stakeholders involved in the reassessment process.

Section 3: General comments

The feedback below pertains to general framework processes that span both the RWE Planning and Drug Selection WG, as well as the RWE Reassessment and Uptake WG. We have combined them below and have responded accordingly.

A few respondents commented that it is a missed opportunity "***if the framework is applied only to currently reimbursed drugs, and not used to shape conditional HTA recommendations for new drugs"***. Other respondents echoed that this framework should expand to "***a broader focus including options for coverage with evidence development that include RWE is warranted"***

> ***Response:*** The WG members appreciate the respondents' comments and want to clarify that the framework is intended to both facilitate early planning of RWE studies prior to funding decisions, and support RWE studies for currently reimbursed drugs where applicable**.** Ideally, the selection, prioritization, and planning steps of the framework are steps that will occur **before** a given drug is funded. While the framework can enable conditional funding, the CanREValue Collaboration members have discussed and reiterated that the CanREValue framework is not intended to lower the threshold of evidence required for drug funding decisions, nor is it intended to change existing HTA recommendation criteria. However, the framework is intended to provide mechanisms for the healthcare system to be more responsive to the evidence available at the time of funding and over the life cycle of reimbursed drugs.

Respondents have highlighted that the barriers to the CanREValue framework include 1) funding sources for RWE projects, and 2) timeliness of RWE generation.

> ***Response:*** The WG members appreciate the feedback from the respondents. The WG members will consider these barriers and potential strategies to address them as they continue to develop and refine the CanREValue framework.

Several respondents suggested that manufacturers, patients, patient groups, and clinician groups should be involved in the working group. One respondent highlighted that this is necessary for the proper implementation of the framework.

> ***Response:*** The WG members acknowledge the importance of engaging with all of the stakeholders mentioned. Currently, several patients are members of both working groups. Moreover, the Engagement WG is undertaking approaches to directly engage with patient groups, clinician groups, and manufacturers more broadly. As the needs of stakeholder groups differ, engagement strategies will be tailored to each group to best suit their needs.

Several respondents proposed that manufacturers should be involved at each step of the framework once it is developed. This includes selecting the drug(s) to evaluate, planning the research study, conducting the research study (gathering and analyzing data), and reassessing evidence.

> ***Response:*** The WG members understand the importance of working with manufacturers throughout this process, from project selection and planning to evidence generation and assessment, while managing relevant conflicts of interest. The mechanisms by which stakeholders will be engaged at each step are still being defined, taking into account the feedback received in this stakeholder consultation. As the working groups develop the details for each specific process within the framework, we will continue to engage with manufacturers regarding our progress and welcome all thoughtful suggestions.

Some respondents suggested the addition of an appeal mechanism to "***protect consistency/transparency***". One respondent suggested that an appeal mechanism would allow manufacturers to include new clinical or economic data.

> ***Response:*** The WG members are committed to ensuring transparency in the development of the framework, as well as the implementation of the framework processes. The WG members will consider the inclusion of an appeal mechanism as they develop the details of the reassessment process. It is expected that the reassessment process will be similar to existing assessment processes, which allow for a number of opportunities for stakeholders to provide input, including pre-submission, input on review, feedback on recommendation, and procedural review.

Several respondents recommended leveraging CanREValue's framework as a mechanism for conditional listing agreements and/or value-based agreements. Moreover, multiple respondents highlighted the need to initiate discussions regarding drug funding early, and potentially initiate interim agreements for risk sharing.

> ***Response:*** The WG members acknowledge the respondents' recommendations and will review this proposal in the next steps of the framework development.

Some respondents raised questions regarding the details of the framework. Questions included: 1) How will differences in funding criteria across Canada be generalized in RWE? and 2) How should both parties resolve the financial uncertainty during re-assessment if a study is completed before the term agreed upon by product listing agreement?

> ***Response:*** The WG members thank the respondents for their questions and will consider these questions during the development of the details of the framework.

Conclusion

This was the second public stakeholder consultation conducted by the CanREValue Collaboration. The CanREValue Collaboration sincerely appreciates the feedback received from all stakeholders. This stakeholder consultation sought to gather feedback on the preliminary CanREValue Framework and how it may be applied to incorporate real-world evidence for cancer drug decision-making.

Prior to this consultation, the CanREValue Collaboration also initiated a public consultation on the Interim Data Working Group Report 2019. Detailed information about this proposal and key points from the discussion summary are provided here. The CanREValue Collaboration has also completed a separate stakeholder consultation for the CanREValue Methods Interim Report. The discussion and feedback summary for the Methods Interim Report will be posted in late 2020.

Next Steps: The CanREValue Collaboration will build and strengthen the framework based on the feedback received and will continue to solicit input as the framework is further refined. In addition, CanREValue Collaboration's Engagement Working Group will continue to engage with stakeholders through future tailored events. The CanREValue Collaboration welcomes any additional feedback regarding the consultation process at canrevalue@cc-arcc.ca.

References

1. CADTH. *CADTH's Proposed Reassessment Framework*.; 2019. https://www.cadth.ca/sites/default/files/cdr/templates/consultations/CADTH_Consultation_Reassessment_Framework.pdf.
2. Health Canada. Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle. https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html. Published 2020. Accessed September 22, 2020.
3. CADTH. *Procedures for the CADTH Pan-Canadian Oncology Drug Review*.; 2020. https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s Drug Review Process/pcodr-procedures.pdf.
4. INESSS. *Evaluation of Drugs for Listing Purposes: A Change of Approach*.; 2018. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Processus/Evaluation_of_drugs_a_change_of_approach.pdf.

Appendix 1: Consultation Questions

1) What barriers do you foresee in the implementation of the framework that is proposed? What potential solutions/facilitators would ensure proper implementation.
    a. In terms of the implementation of this framework: who should participate in the reassessment of a drug that is currently publicly funded?
    b. What role should each stakeholder have in the reassessment process?
    c. In an ideal scenario, what do you foresee your role being in the process of reassessment for a drug that is currently publicly funded?
    d. How should the results from a reassessment be disseminated to different stakeholders or the public?
    e. Should different criteria be used to re-assess a drug compared to when it is assessed for the first time? If so, which criteria should be different?

2) What benefit/opportunities do you anticipate for your organization or the healthcare system if there was a mechanism to re-review a drug that is currently publicly funded?

3) As we are in the planning stage of the CanREValue proposal for a reassessment process, we welcome collaboration and engagement from interested stakeholders. Please indicate how you would like to be involved in the development and implementation of this proposal.

Appendix 2: Quantitative Summary of Feedback Reports Received for Data WG Interim Report

Category:	**Organization**
Academic Research	Pediatric Oncology Group of Ontario (POGO)
	PGTM (Programme de Gestion Thérapeutique des Médicaments)
	Queen's University
Pharmaceuticals companies and/or associations	Bayer Inc.
	Astellas
	BMS
	Janssen Inc.
	Pfizer Canada ULC
	Roche
	AstraZeneca Canada
	Merck Canada Inc.
	Servier
	Innovative Medicines Canada & BIOTECanada
Industry-related Consultancies	PDCI
	Innomar Strategies
	Pulse Infoframe
Patient Group	Individual Patient
	Canadian Breast Cancer Network
	Ontario Lung Association
	Save Your Skin Foundation
Other	Participants with HTA experience