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

CanREValue Collaboration Methods Working Group Interim Report 2020:

Response to Stakeholder Consultation for Progress Report on Real World Survival Data

Introduction and Background

On March 23rd, 2020, the Canadian Real-world Evidence for Value in Cancer treatments (CanREValue) Collaboration initiated a public stakeholder consultation regarding the interim report drafted by the CanREValue Methods working group (WG).

During the stakeholder consultation, the CanREValue Collaboration sought feedback regarding the preliminary report. Throughout the consultation period, which remained open until April 19th, 2020, we received a total of 13 responses from different stakeholders (Table 1).

Table 1: Summary of respondents

Category	**Total Number of Feedback Reports Received (N=13)**
Pharmaceutical Companies	9
Industry-related organizations	2
Academic/Researcher	1
Patient Group	1

The CanREValue Collaboration sincerely thanks the respondents for their submitted feedback and recommendations. Along with the Method 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. A summary of the feedback, as well as revisions to the interim report, are described throughout this document.

Summary of Feedback

Theme 1: Methods or topics that CanREValue should expand on related to future methods or data work

1. We received a number of suggestions to explore a variety of methodological topics and areas for future work. Some respondents asked how a method would be determined to be "good enough". Stakeholders highlighted the importance of developing methodological standards to ensure the quality of real-world evidence (RWE).

Response: We were excited to see such keen interest in the area that also aligns with our hope to develop tools to support the methodological rigor of RWE in Canada. Future work must explore developing broader guidance on methodological standards similar to what is available for other technical areas in HTA, such as economic evaluations, and we look forward to exploring opportunities to work collaboratively in this area. We will continue to champion the need for methodological standards.

2. A number of suggestions were given to explore expansion to other topics and methodologies that can augment or help overcome some of the limitations listed in the report. These include the suggestions to explore fractional polynomials, use of negative controls, sensitivity, time-varying co-variate analyses, principal stratification, latent variable, factor models analyses. Moreover, some feedback noted that the integration of clinical trials and observational studies may be relevant because applications of network meta-analysis (NMA) and match-adjusted indirect comparison (MAIC) are already widely used to integrate information across controlled trials and observational studies.

   Response: These suggestions will be discussed internally in the Methods Working Group as we continue to develop methods guidance for the CanREValue framework. Importantly, the interim CanREValue Methods report and this response document have been made public to help also spur others in the RWE space to consider development of similar work to help advance methodological quality in RWE.

3. Stakeholders suggested we include mention of patient reported outcomes (PROs) as an important metric. They highlighted that the value of some oncology regimens may be more associated with its impact on PROs improvement or PROs stabilization rather than survival. Methods could be considered to be applied for PROs in real-world data (RWD) collection and analysis.

Response: We agree that PROs hold important value, and agree that improvements and stabilizations in PROs are important measures that can inform decision-making. That said, in context of the current report which focuses on survival as an outcome, a discussion of methodology related to PROs is currently out of scope.

4. Though the report in question focuses on methods, a number of respondents flagged important data limitations that exist with currently available data in Canada. Specifically, data on biomarkers, lifestyle factors, disease staging, tumor-types may not be available, which could affect the quality of comparative effectiveness analysis, regardless of method used. Suggestions were given to consider partnerships with industry to facilitate building RWD infrastructure or leveraging existing data infrastructure (e.g., patient support programs, patient registries, etc.) or linkage with larger multi-national cohorts.

   Response: We agree that the current data holdings in many Canadian jurisdictions may have important gaps, depending on the analysis being conducted. Much of the feedback were raised during the consultation on the Data WG Interim Report launched in December 2019. Since then, our thoughts and responses have been extensively highlighted in the response document that was posted in 2020. We continue to work with data partners to identify data gaps and develop more robust data collection. We continue to explore potential collaborations and work to help build on established data infrastructures and believe that many of the ongoing national initiatives will greatly improve the available oncology data.

Theme 2: Critiques of the Current Methods and Request for Further Changes

1. A number of comments suggested further insights on propensity scoring methods cited in our reports and their use in RWE. Specifically, applications and best practices of the use of propensity scores such as weighting, specification, assessing overlap, and assessing balance.

   Response: Propensity scores have become a standard in many real-world evidence-based studies. We agree with the suggestions made that it is important to understand the best-practices of the methodology and ensure that propensity scores are being optimized and not inappropriately applied. Importantly, we know that when applied incorrectly they can introduce bias. We have added the need to align with best standards and added citations of seminal papers and guidance that have already extensively described the use of propensity scores.

2. A number of suggestions and comments received suggested that the current plan had an overreliance on overall survival (OS). They expanded on this by suggesting that patients do not solely value survival, but survival linked to meaningful quality of life measures. Some comments suggested inclusion of other endpoints measured in trials which may be important to explore through RWE, such as progression free survival (PFS) or time to treatment discontinuation. Additionally, some stakeholders highlighted that OS would take considerable time to assess for certain types of cancers, especially early cancers and cancers with longer survival periods.

   Response: We appreciate the feedback and suggestions around the use of OS. We understand the limitations and considerations when using OS as the primary outcome and have aimed to highlight in the report a number of these considerations. OS is considered an important current standard used both clinically and in HTA and we strongly believe that for RWE to hold true value it must align with current standards. OS is a reliable and objective endpoint for assessing clinical effectiveness, ascertainable in administrative data, and an important outcome to stakeholders. Lastly, we do not believe that the use of OS as the primary outcome would preclude or negate the use of other important outcomes such as PFS or quality of life. It will be important in future work to examine other outcomes beyond OS, and appropriate methods will be determined and presented as that work is being undertaken.

3. We received feedback that treatment sequencing could have a significant impact on the results. Specifically, one stakeholder highlighted that variables can also be quite different between provinces depending on what therapies are reimbursed and with what criteria. They suggested treatment sequence be considered when comparing RWE results across provinces and identifying analytical limitations.

Response: We are thankful for this suggestion and agree that this is an important area for consideration when designing the study. We have added this important point and suggestion to the report.

4. Is there an a priori preferred method of the ones summarized in the document? A table summarizing the advantages and disadvantages of these methods and in what circumstances one would be preferred over the other would be useful.

   Response: While the literature does have examples of different methods, the WG is working on developing Canadian experience using a variety of methods. Our experience using readily available administrative data will inform future recommendations in the Canadian oncology pharmacoepidemiologic space.

5. Suggestions were made to add mention of the accuracy of date of death. It was noted that the date of death may be accurately documented in most cases, such as for patients that are censored for survival, but censoring patterns may follow a specific distribution due to data collection methods. Appropriate correction methods may need to be applied.

   Response: We have included this important consideration to the report.

6. Suggestions highlighted potential issues associated with patients with very high body weight should be further described as a potential limitation of this analysis that would limit the interpretation.

   Response: We have added this potential concern to the document for issues to consider when conducting analyses.

7. Stakeholders suggested that we discuss the impact of channeling bias. This is an important consideration for analyses of newly marketed medications.

   Response: We agree on the importance of addressing factors that could lead to baseline differences between groups. We have included that treatment sequence and reimbursement policy must be accounted for to reduce the risk of bias to the design. We have added this example in the document as a good example of potential selection bias.

Theme 3: Comments Regarding the Larger Framework Process/Critiques of CanREValue

1. We received a number of suggestions that were related to the broader framework. A number of suggestions were made to help CanREValue further improve our access, transparency and timelines to be addressed in subsequent reports. There were specific comments that were related to the Policy WG report. Additionally, stakeholders highlighted the importance of continuing to engage industry and patients and leverage their experience and expertise in RWD/RWE.

   Response: We are delighted to continue to receive such extensive engagement from many stakeholders. We continue to work to improve our engagement strategy and all recommendations have been presented to the Engagement working group. As part of this response, we are working to further expand our engagement strategy, specifically with the private sector to ensure that we achieve our goal of developing a robust framework that is transparent.

2. Specific suggestions have been made to align with global RWE framework efforts (Health Canada, FDA, and EMA RWE).

   Response: As previously stated in other reports, we do aim to do our best to align with global standards. It is important to note that no framework will perfectly align as we must (and should) account for the Canadian context with respect to data availability, privacy laws, and healthcare system structures including new changes to the system.

3. There were a number of suggestions to help tackle the overall issue of transparency of RWE projects. Suggestions included that code used for any analysis to be made public, the code be reviewed by regulatory agencies similar to RCTs, and data should be anonymized and made public (perhaps in a secure venue) as to allow verification of the analysis.

   Response: We strongly agree that transparency in any implementation of RWE will be essential to ensure the public's trust in the process. Learnings from current global practices in RCTs is an important suggestion. We will present all suggestions to our working groups as we continue to work to develop the framework. It is important to note that any framework proposed by CanREValue is a proposal and the final implementation will have to be determined by regulators, payers, and HTA agencies.

4. Due to the relative rarity of childhood cancers, stakeholders highlighted an important gap with respect to sample sizes in pediatric studies. Compared to adult cancer studies, pediatric studies are based on smaller sample sizes. As such, stakeholders suggest that perhaps RWE may have a role in helping address this vital gap.

Response: We agree that RWE may hold an important place in filling some of the information gaps that exist with pediatric cancers. Although we have not specifically highlighted the pediatric population, the limited RCT evidence and rarity make for an important use-case. We will communicate this to our stakeholders.

Conclusion

The CanREValue Collaboration sincerely appreciates the feedback received from all stakeholders to the third public stakeholder consultation. This consultation focused on gathering feedback on the progress of the Method WG, with respect to the survival data.

Prior to this consultation, the CanREValue Collaboration also initiated two public consultations consultation on the Data Working Group Interim Report 2019 and the Policy Working Groups Interim Report 2019.

Next Steps: The CanREValue Collaboration will continue to build a framework based on the feedback received. Moreover, we 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.

Appendix 1: Quantitative Summary of Feedback reports Received for Methods Interim Report

Category	Organization	Total Number of Responses Received (N = 13)	% of All Feedback Received
Pharmaceutical companies	Bristol Myers Squibb Canada	9	69%
	Bayer		
	Pfizer Canada		
	Merck Canada		
	Janssen		
	Roche Canada		
	Servier Canada		
	Innovative Medicines Canada		
	Amgen		
Industry Related Organizations	Aetion	2	15%
	Quality HTA		
Academic Research	Pediatric Oncology Group of Ontario	1	8%
Patient Group	Save Your Skin Foundation	1	8%