When should the conduct of RWE studies be prioritized for reimbursement purposes? Insights from Canadian and global stakeholders

HTA32

Boss J[1], Shulak L[2], Rao T[2], Tam C[1], Sullivan SM[3]

[1]Evidera, London, UK; [2]Evidera, St-Laurent, QC, Canada; [3]Evidera, Ivry-sur-Seine Cedex, Île-de-France, France

Introduction

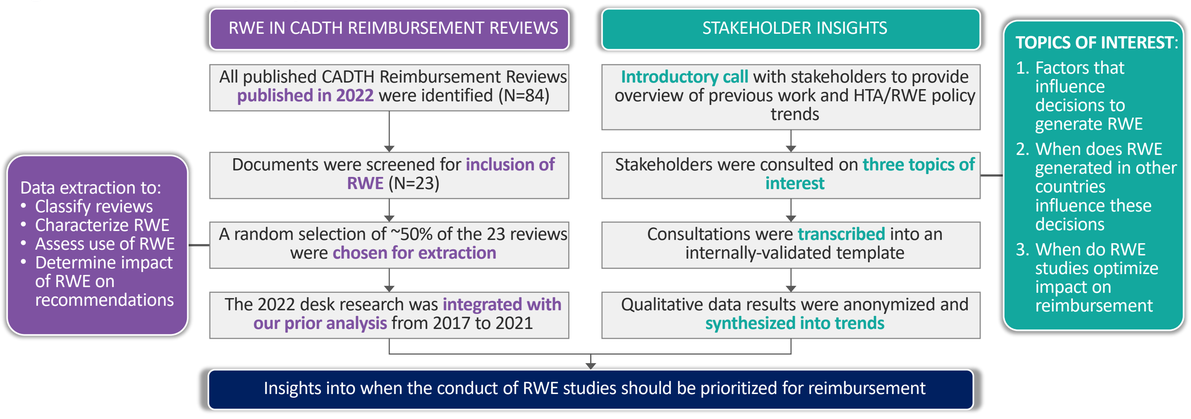
- Canada aims to be one of the first jurisdictions to implement and leverage real-world evidence (RWE) throughout the drug life cycle to inform market entry and reimbursement, as detailed in the Canadian Agency for Drugs and Technologies in Health (CADTH) 2022 to 2025 strategic plan[1].
- In 2023, CADTH partnered with Health Canada and Institut national d'excellence en santé et services sociaux (INESSS) to create the "Guidance for Reporting Real-World Evidence"[2]. This guidance[2] aims to promote standardization in RWE reporting by providing core conduct and reporting standards for RWE studies of health technologies being submitted for regulatory approval and/or reimbursement.
- While health technology assessment (HTA) bodies and regulatory agencies globally are increasingly implementing RWE in healthcare decision-making and publishing guidance on the standardization of RWE study reporting[2,3,4], uncertainty remains about when RWE evidence generation should be prioritized and conducted for reimbursement purposes.

Objectives

- We conducted our study in two parts, with the following objectives.
  - **RWE in CADTH Reimbursement Reviews**: To build on our previous work[5] identifying CADTH Reimbursement Reviews that included RWE with the aim to understand how RWE has been considered in recent Canadian HTA.
    - We updated our previous analysis of CADTH Reimbursement Reviews from 2017 to 2021 with 2022 data.
  - **Qualitative Research on Stakeholder Insights**: To collect insights from three stakeholder groups (Canadian and global), including pharmaceutical industry representatives, payers/HTA decision makers, and patients/patient advocates, on when the generation of RWE should be prioritized for reimbursement.

Methods

Figure 1. Overview of study methods



Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; HTA = health-technology assessment; RWE = real-world evidence

Qualitative Research on Stakeholder Insights:

- The following three topics of interest were discussed:

TOPIC 1

Factors that influence decisions to generate RWE:
- The magnitude and type of value the stakeholder hopes the RWE can provide for their needs
- Feasibility of conducting an RWE study
- The impact RWE has on clinical benefit and/or cost-effectiveness outcomes

TOPIC 2

When does RWE generated in other countries influence these decisions:
- How the decision is influenced
- Any specific countries that the stakeholder prefers using RWE from to inform their decisions and why
- If RWE was generated due to requests by regulatory or reimbursement agencies

TOPIC 3

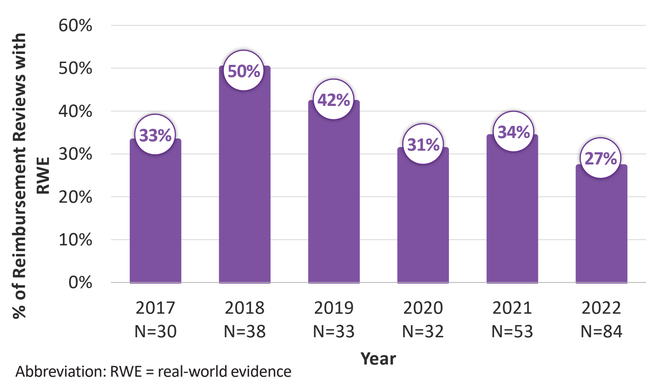
When do RWE studies optimize impact on reimbursement:
- What type of studies are the most influential
- What types of data and outcomes
- What therapeutic areas and treatment setting

Results

Inclusion of RWE in CADTH Reimbursement Reviews by Submission Type and Year

- Trends in the inclusion of RWE over time were not observed.
  - Approximately 27% of initial CADTH submissions included RWE in 2022; approximately 36% of submissions included RWE across the full six-year period from 2017 to 2022 (**Figure 2**).
- Similar trends were observed in 2022 as in previous years for top therapeutic areas and use in rare diseases.
  - RWE was most frequently used in reviews of technologies in oncology, genetic disorders, and neurology.
  - Approximately 40% of reviews for rare diseases included RWE in 2022; approximately 38% of reviews for rare diseases included RWE across the full six-year period from 2017 to 2022.
- Across the full six-year period from 2017 to 2022, approximately 32% and 15% of reviews included RWE in the clinical/combined report and economic report, respectively.
- CADTH recommended generation of RWE for approximately 5% of reviews, all of which occurred between 2017 and 2021, and mainly for initial submissions rather than resubmissions.
- In 2022, RWE influenced CADTH recommendations approximately 50% of the time. RWE was most often generated to fill gaps in randomized controlled trial evidence; other evidence gaps included long-term follow-up data, systematic review evidence, and comparative efficacy evidence. In some cases, the RWE was criticized for being inconclusive due to limitations in study design and analysis.

Figure 2. Inclusion of RWE in CADTH reimbursement reviews over time



Abbreviation: RWE = real-world evidence

Thematic Analysis of Stakeholder Insights in Qualitative Research

- An overview of study participants is presented in **Table 1**.
- For analysis purposes, payers/HTA decision makers and patients/patient advocates are considered together as non-industry stakeholders.
- Stakeholders aligned on several themes related to each of the three topics of interest. An overview of the high-level themes obtained from the consultations with stakeholders is presented by topic in **Table 2**.

Table 1. Stakeholder groups represented in qualitative research (N=11)*

Role	• Industry stakeholders (n=9) • Non-industry stakeholders (n=2)
Region	• Canadian perspective (n=9) • Non-Canadian regional perspective (n=4 including Europe and APAC)

*Note: totals may not be equivalent as some regional allocations overlapped

Abbreviation: APAC = Asia-Pacific

References

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Results (cont'd)

Table 2. Key themes from stakeholder insights by topic

THEME	THEME DESCRIPTION
Topic 1—Factors influencing decisions to generate RWE	
Need for RWE that is complementary to RCT data	RWE alone is not sufficient for reimbursement; however, RWE can add value by being complementary to RCT data. For example, RWE can be used for validation of RCT results or to explore RCT outcomes in a larger or different patient population to support new indications
Need for burden of illness data	RWE studies can be useful to generate "burden of illness" data that is important for reimbursement, including epidemiology data, economic model inputs, and insight into patient unmet need
Likelihood of HTA acceptance	Stakeholders consider how likely HTA bodies are to accept RWE
KOL (payer, clinician) perspective	Stakeholders consider the perspective of key opinion leaders on RWE, including payers and clinicians
Data access/availability Timing of HTA submission	Data access and availability are important factors related to the feasibility of being able to generate RWE, and to generate RWE in time for HTA submission
[Industry-specific theme]: Reimbursement distinct from regulatory for RWE generation	RWE generated for reimbursement may be distinct from that generated for regulatory approval, or may require alignment across cross-functional teams, depending on the organization
[Industry-specific theme]: Global strategy is considered in regional-level objectives	Regional affiliates consider the global team's strategy for RWE when thinking about local RWE evidence generation plans
Non-industry stakeholder on Topic 1: "*You can't use RWE to supersede RCT trial data in any population including primary prevention. You can use it to complement your value proposition but never supplant.*"	
Topic 2—Influence of RWE generated in countries outside Canada	
Canadian-specific data is preferred	Canadian-specific data is preferred for reimbursement
Data from outside Canada should be generalizable to the Canadian market	If not available or feasible to generate Canadian-specific data, then RWE used from outside of Canada should be generalizable to the Canadian market
Justify lack of Canadian RWE	Justification should be provided to HTA bodies for why Canadian RWE is not being utilized
UK is preferred if Canadian-specific data is unavailable	RWE from the UK is generally preferred for data from outside of Canada based on the similarities in healthcare systems and patient access
Industry stakeholder on Topic 2: *"Data access I think is definitely a challenge in Canada."*	
Topic 3—RWE studies that optimize impact on reimbursement	
Quality-of-life/patient-reported outcomes	These study types and outcomes are those that could have the greatest impact on reimbursement decision making
Healthcare resource use	
Long-term clinical outcomes	
Treatment patterns	
Burden of illness	
Industry stakeholder on Topic 3: *"When you have tons of clinical uncertainty or your trial hasn't conducted that type of evidence, RWE is incredibly powerful."*	
Additional themes across stakeholders not specific to Topics 1 to 3	
Need for more guidance on RWE	More guidance on RWE for reimbursement is needed; the CADTH guidance[2] on RWE focuses more on methodology for HTA submissions, rather than how the data will be used and interpreted in reimbursement decision making
Need for early engagement with payers/HTA decision makers	Early engagement with payers and HTA bodies is important for identifying relevant evidence gaps that can be filled by RWE and for gaining insight into optimal study design
Non-industry stakeholder quote: "*Up to a number of years ago the patient voice was never heard at these meetings. When you went to the approval, HTAs, the patient wasn't there, the patient advocate wasn't there.*"	

Abbreviation: CADTH = Canadian Agency for Drugs and Technologies in Health; HTA = health technology assessment; KOL = key opinion leader; RCT = randomized controlled trial; RWE = real-world evidence

Stakeholder-specific Insights from Qualitative Research

- Several stakeholder-specific insights regarding type or geographic perspective were obtained during the interviews.
  - It was discussed that it is important to incorporate different stakeholder perspectives into RWE generation including patients, clinicians and payers. Industry stakeholders frequently discussed the importance of RWE being able to increase the likelihood of HTA acceptance.
  - For some industry stakeholders, RWE planning for reimbursement is distinct from RWE planning for regulatory approval, while for others, alignment of RWE planning across market access, regulatory, and other cross-functional teams is considered essential.
  - When asked about the types of RWE studies that optimize impact on reimbursement, quality-of-life and healthcare resource use studies were identified by almost all stakeholders, whereas studies assessing long-term clinical outcomes, treatment patterns, and burden of illness were identified only by industry stakeholders.

Discussion

RWE in CADTH Reimbursement Reviews

- Addition of 2022 data to our previous work identifying CADTH Reimbursement Reviews that included RWE (2017 to 2021) resulted in similar findings. There was no trend in the inclusion of RWE over time and the most common therapeutic areas for RWE inclusion remained the same (oncology, genetic disorders, and neurology). In 2022, RWE was included in approximately one quarter of initial CADTH submissions, indicating that there may be opportunity for greater utilization of RWE in reimbursement reviews in Canada.
- Trends were surveyed over a number of years; however, limitations of this analysis include variability in the definition of RWE used in the CADTH reports, which may have led to undercounting the number of reviews with RWE if not clearly documented. Additionally, assessing the influence of RWE on CADTH reimbursement recommendations is subject to interpretation.

Stakeholder Insights on the Prioritization of RWE for Reimbursement

- Overall, stakeholders were aligned on the value RWE can provide as complementary evidence to support data generated from RCTs, to fill a gap left by the RCT, or to validate results from the RCT in a larger and/or different patient population.
- For reimbursement in Canada, stakeholders agreed that local Canadian data is preferred; however, data availability and accessibility often limit the feasibility of generating such data.
- Industry stakeholders consider the likely acceptability by HTA bodies and payers when making decisions about RWE generation and noted that this may vary by region (e.g., Canada, Asian-Pacific countries, European countries).
- Stakeholders highlighted the importance of capturing the patient perspective in RWE, as this type of data can provide valuable insight into the patient and caregiver experience – insight that until recently had not been routinely encouraged or considered for reimbursement decision making.
- Non-industry stakeholders emphasized that RWE should be robust and generated in studies conducted with a high degree of methodological rigor.
- A key limitation is the small sample size for the stakeholder consultations and predominance of industry versus other stakeholders invested in HTA and reimbursement processes. As such, the insights presented in this research are high level and did not allow for in-depth analyses; also, they may not be representative of all stakeholders of a given type or regional perspective.

Conclusions

- While our research highlights important areas of consideration for RWE prioritization in the context of reimbursement, further research is needed to fully explore these questions across a larger sample of stakeholders.
- Current guidance provided by HTA bodies and regulatory agencies globally focuses on RWE methodology, but there is a need to further support the practical implementation of RWE for reimbursement.
- A framework that helps stakeholders prioritize when to generate RWE for reimbursement purposes would provide value and could be tailored to different countries/regions and stakeholders.
- Next steps include more in-depth qualitative analyses of the current data set, cross-country/regional comparisons in key markets, and expansion of stakeholder involvement in the development of such a framework.