The Use of Real-World Evidence in Health Technology Assessments
by the Canadian Agency for Drugs and Technologies in Health
Key Messages

- RWE can inform decision-making in HTA appraisals and uncertainties in the real-world value of medicines
- In a recent review of CADTH HTA submissions, approximately one third have incorporated RWE in some capacity
- Many uncertainties arising from CADTH HTA appraisals can be informed by RWE
- A framework or guidance around use of RWE in HTA is necessary to ensure proper methodology

Abstract

Real-world evidence (RWE) has the strong potential to inform decision-making in health technology assessments (HTAs) and to inform uncertainties in the real-world value of medicines. In Canada, the national organization that governs HTAs is known as the Canadian Agency for Drugs and Technologies in Health’s (CADTH). Since 2012, approximately one third of CADTH HTA submissions have used RWE in some capacity, such as informing economic cost inputs or creating indirect treatment comparisons. Many of the uncertainties arising from CADTH HTA appraisals can be mitigated using RWE, although more groundwork in creating a framework and proper methodology for RWE use in HTA submissions is necessary.

Introduction

In the era of big data, real-world evidence (RWE) has become an emerging concept in healthcare research. While the field is still evolving, the broad definition of RWE is information on health outcomes and healthcare derived from sources outside of clinical trial settings. These include electronic health records, claims and billing data and medical charts, among others. The use of RWE has the potential to inform decisions across the product development lifecycle, particularly as the regulatory approval and reimbursement agencies become increasingly interested in real-world efficacy and safety, healthcare utilization, and costs. While randomized controlled trials (RCTs) are still considered the gold-standard for evidence generation, RWE is increasingly becoming a source of evidence where RCTs face limitations.
The richness of Canadian data lies primarily within its provincial datasets, which capture detailed real-world data (RWD) – such as disease outcomes and treatment patterns – and can be linked at the individual level using unique patient identifiers. Research efforts to create research data infrastructure that can support multi-province RWE studies are currently underway, however, at this time, difficulties in cross-provincial data linkage limit RWD analysis to an intra-provincial level and may thereby limit the type of data that can be presented, for example, in drug reimbursement submissions. While high-level RWE on unmet need and disease burden may be obtained through national-level surveillance datasets (such as those available through the Canadian Institute for Health Information), more detailed data on patient profiles, health utilization costs, as well as data on drug safety and effectiveness may only be examined at the provincial level.

**RWE and CADTH**

Canadian public drug reimbursement recommendations are made through the CADTH’s Common Drug Review (CDR) and pCODR (pan-Canadian Oncology Drug Review) processes, which conduct HTAs of non-oncology and oncology drugs, respectively. The CADTH Submission Guidelines state that all evidence is considered for drug submission. In particular, the use of non-RCT evidence can be useful in informing uncertainties arising from lack of long-term follow-up from clinical trials to evaluate persistence of clinical efficacy and safety. This can be when an RCT is considered unfeasible due to a limited number of patients or an RCT is unethical, when RCTs lack relevant comparators, or when there is uncertainty in the real-world use of a treatment (e.g. its dose and duration) or its effects in a real-world population, due to the stringent inclusion and exclusion criteria of most clinical trials.

CADTH recently published an environmental scan on the use of RWE in drug technology assessments by HTA and regulatory organizations around the world. The report provided an overview of types of the eligibility criteria for RWE, as well as current use in different regulatory and HTA organizations. Unfortunately, it did not provide any insight into CADTH HTA submissions beyond a review by Griffiths et al., which included the use of single-arm clinical trials.
Looking to understand the nuances of how RWE has informed recent Canadian reimbursement decisions, Medlior Health Outcomes reviewed CADTH HTA submissions from both the CDR and the pCODR from January 1st, 2017 to May 22nd, 2018 to examine which submissions used RWE and where RWE could be used to inform uncertainties in the appraisals. This review included 43 completed CDR submissions and 33 completed pCODR submissions.

Current Use of RWE in CADTH HTAs

Through the CDR, there were a total of 18 submissions that used RWE in some form, whether it was to inform costs in economic models, or the use of historical cohorts for indirect treatment comparisons, among other uses. Of these, 2 were approved, while 16 were conditionally approved for reimbursement (Figure 1). Similarly, through the pCODR, there were a total of 8 submissions that used RWE: 1 was approved and 7 were conditionally approved. To the extent there exists a general theme amongst these appraisals, the conditional reimbursement recommendations made by CDR and pCODR have hinged upon general requirements to improve the cost-effectiveness of the drug, rather than any specific need to reduce the uncertainty associated with the magnitude of its clinical benefit.

Figure 1: Use of RWE in completed CADTH HTA submissions from January 1, 2017 to May 22, 2018. A) Common Drug Review appraisals B) pan-Canadian Oncology Drug Review appraisals.
Submissions to CDR that have utilised RWE did so primarily to inform the economic analyses, whereas the submissions to pCODR used RWE to inform the economic analyses in addition to providing comparative effectiveness evidence. For example, one pCODR submission in 2013 (axitinib for the treatment of metastatic renal cell carcinoma after failure of a prior systemic therapy with either a cytokine to sunitinib) was revised in 2017 following a Request for Advice from pCODR to compare axitinib to everolimus as second-line therapy. This comparison was requested because the reimbursement recommendations for axitinib for this indication differed among Canadian provinces at the time, with some provinces offering the choice of either everolimus or axitinib as second-line treatment and other provinces mandating a trial of everolimus prior to requesting funding for axitinib. The resubmission to pCODR provided evidence from several retrospective observational studies comparing axitinib to everolimus as second-line treatment, and ultimately received a positive reimbursement recommendation. This approach to integrating RWE in an HTA of axitinib was different from the one undertaken by NICE (TA 333), where RWE was used to provide an alternative indirect comparison of sorafenib or axitinib and best supportive care in a patient group that has previously received the NICE-recommended first-line treatment for this indication (sunitinib). This different use of RWD to support the same drug and indication across the two countries illustrates that a country-specific approach to integrating RWE in drug HTAs is likely necessary.

Another example of RWE in a pCODR submission used RWE to allow comparison of direct evidence from single-arm clinical trials with indirect evidence from previous studies to evaluate the efficacy of an intervention (alectinib for anaplastic lymphoma kinase-positive (ALK+), locally advanced or metastatic non-small cell lung cancer (NSCLC)). When a direct treatment comparison through a randomized controlled trial are not available (as in the case of rare diseases or where it would be unethical to conduct one), individual patient data can be used to construct a synthetic control arm for comparison to a single-arm clinical trial. Applying inclusion/exclusion criteria from a clinical trial to RWE can generate similar patient populations, resulting in comparable data sources. Statistical techniques can also be employed to help validate the comparability of the populations. As such, the estimates derived from RWE can form a “synthetic” control arm which allows comparison to typical RCT data. This method remains unbiased if the two trials are sufficiently similar, and if the same treatment effect is measured in both trials. However, the indirect estimates must not be subject to statistical bias.
Results of the synthetic control arm study in the alectinib pCODR submission were published recently in June 2018 by Davies et al. The majority of ALK+ NSCLC patients on ALK-inhibitor crizotinib experienced disease progression within the first year. To satisfy the need for additional therapy, two new drugs were approved in the crizotinib-failure setting: alectinib and ceritinib. To compare effectiveness of alectinib vs. ceritinib, data from two single-arm alectinib trials were pooled (global and North American studies; n=183) and the ceritinib arm was derived using electronic health records (EHR) from the US-based Flatiron Health database (n=67). Inclusion and exclusion criteria from the alectinib clinical trials were applied to the EHR to define a comparable ceritinib population. Propensity scores were applied via inverse probability treatment weighting to reduce bias and ultimately balance the two cohorts to ensure similarity.

The median overall survival for alectinib patients was significantly longer than the overall survival of ceritinib patients. A multivariate Cox model showed that alectinib was associated with a statistically significant lower risk of death. A sensitivity analysis was conducted that compared an independent clinical trial cohort of ceritinib patients with the ceritinib RWE, to assess the generalizability of the RWE to a clinical trial population. The RWE and independent trial groups had similar median overall survival values, demonstrating that the estimates from the RWE were generalizable. Carefully considered studies such as Davies et al. showcase the high impact potential of RWE in a clinical setting. This powerful application of RWE can be further utilized in HTA to inform decision-making.

**Potential Use of RWE in CADTH HTAs**

Among the uncertainties highlighted in the CDR and pCODR appraisals, there were several common categories (Figures 2 and 3). It is worth noting that many reviews pointed out multiple uncertainties, therefore the total number of uncertainties listed below is greater than the total number of appraisals.

![Figure 2. CADTH CDR uncertainties that RWE can inform from a total of 43 completed appraisals between January 1, 2017 to May 22, 2018.](image)
The most common uncertainties reported were in the magnitude of demonstrable clinical benefit, due to trial limitations such as small sample sizes or analysis (such as the methods used to account for missing data), as well as a lack of the necessary comparative data, resulting from either single-arm trials or trials against a different comparator. As clinical benefit is often a key driver of cost-effectiveness, uncertainty in its magnitude was commonly cited as causing an underestimate the incremental cost-effectiveness ratio (ICER).

There was a common concern expressed regarding uncertainties over whether the long-term efficacy and safety would be different than the results reported in clinical trials, typically because the trials provided no long-term data themselves. Similarly, there are often uncertainties in the generalizability of results from clinical trials to Canadian populations, given that they take place in other countries, or only include a subset of a real-world patient population. Differences between clinical trial and real-world treatment settings also create uncertainties in in duration or dosage of treatment.
Many of these uncertainties could be mitigated by using RWE, given the right data and environment. For example, the length of time the drug has been on the market or the availability of relevant comparators would be considerations necessary for the use of RWE in HTA submissions. If all required data are available, RWE can provide valuable insights into the generalizability of the data to real-world populations, as well as the effectiveness of a drug and the duration/dosage of treatment outside of clinical trials. In particular, RWE can be used to provide evidence on the sequencing of available oncology therapies due to the multiple lines of therapy used in the real world that may not be examined in clinical trials.

**Impact and Limitations of RWE**

Reimbursement recommendations made through CADTH’s processes are non-prescriptive, and payers make the ultimate decision as to whether or not to fund the drug. In effect, drugs that have received a negative recommendation from the CADTH processes may still be listed in the provincial and national formularies through Product Listing Agreements (PLAs) negotiated with the product manufacturers individually or collectively through the Pan-Canadian Pharmaceutical Alliance (pCPA).13 As these agreements are confidential, it is difficult to understand the role that RWE may play in these negotiations. Furthermore, Canada does not have an equivalent of the UK’s Cancer Drug Fund (CDF), which could facilitate access to drugs in the interim while more data on the safety and effectiveness of the drug in the routine clinical setting is collected. Nevertheless, RWE represents an expanding area of opportunity for all parties involved in the drug reimbursement process.

However undefined it may be, HTA agencies are increasingly recognizing the need for RWE in drug-funding decisions. The use of RWE becomes more routine in HTA submissions, a collaborative approach between industry, government, payors, providers and patients is necessary to ensure appropriate use of RWE. RWE can be highly informative and valuable in determining the value of medicines; however, limitations to its use do exist. Data quality is of general concern due to missing or invalid data from real-world data sources, and there are outcomes that are not captured through electronic health records, such as patient-reported outcomes. Furthermore, as in all non-RCTs, bias and confounding are generally present in RWE studies; however, statistical methods exist to adjust for bias and algorithms or proxies can be used to model outcomes of interest. Further methods development to address limitations of RWE is necessary to facilitate its use in HTAs.

There is currently no framework or guidance for the use of RWE in HTA. A multi-year initiative funded by the Canadian Institutes of Health Research has begun to develop a framework for the use of RWE into oncology drug-funding decisions in Canada.14 In the meantime, performing RWE studies with appropriate methodology and statistical analysis can help shape the use of RWE in HTA submissions.
Conclusions

With the increasing awareness of RWE in HTA submissions, RWE has the potential to influence decision-making in drug reimbursement by HTA agencies such as CADTH. While RWE has been accepted in HTA submissions in Canada, RWE has the potential to play a much larger role. With the ongoing development of a framework for the use of RWE in Canada, it is likely that the use of RWE will continue to increase. In the absence of this framework at present, RWE is still currently being used to provide evidence for HTAs in Canada and the United Kingdom, and advances in the use of RWE as an input into HTA decision-making are being driven by those willing to explore its potential in facilitating positive reimbursement decisions from HTA agencies.

About Us

As an independent Canadian consultancy based in Calgary, Alberta, Medlior offers a variety of research services, as well as access to and expertise with Canadian RWE databases. We collaborate with experienced biostatisticians and epidemiologists from academia and the health system to provide expertise in Canadian provincial and national data sets, surveys, and patient reported outcomes to answer your research questions. Medlior is experienced with both the UK and Canadian HTA processes and can support you in integrating RWE into your HTA projects.

Driven by scientific expertise and powerful analytics, Medlior brings value and insights to every research project by working in close partnership with our clients to understand their needs and objectives. Email us at tara.cowling@medlior.com to set up an appointment and get more information on how we can customize our services to meet your research objectives, timeframes, and budgets.
References


