Real World Evidence – What role can it play in real world decision-making?

Backgrounder

INSTITUTE OF
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The Institute of Health Economics (IHE) is an independent, not-for-profit organization that performs research in health economics and synthesizes evidence in health technology assessment to assist health policy making and best medical practices.

This small roundtable was organized by the Institute of Health Economics, IHE, and is supported by Eli Lilly Canada Inc. Eli Lilly Canada Inc. is part of a global, publicly traded life sciences company (Eli Lilly and Company) committed to making "medicines that help people live longer, healthier, more active lives." With headquarters in Toronto, ON, the pharmaceutical division of Eli Lilly Canada Inc. employs nearly 400 people across the country

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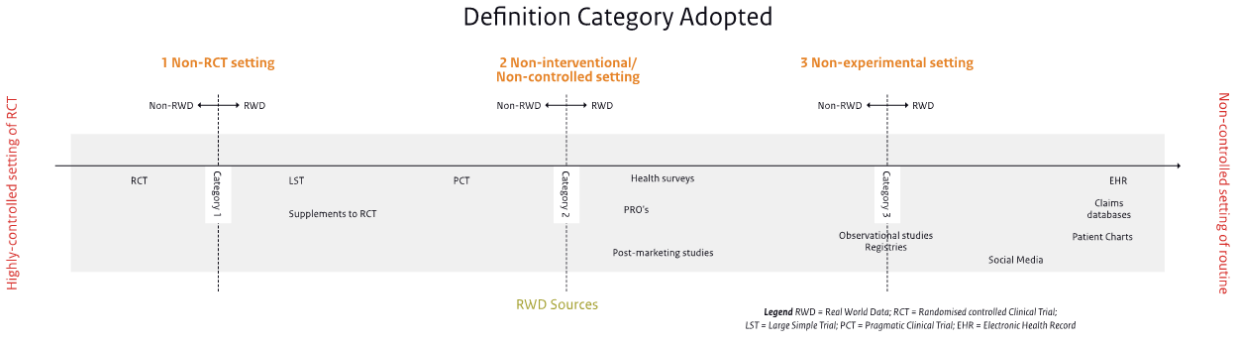
Overview and definitions of real-world evidence

"Real-world evidence" is a term that is becoming increasingly used. Other terms closely associated and sometimes used interchangeably are "real-world data", "observational data", and "real-world effectiveness". The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defines real-world data as "data used for decision making that are not collected in conventional randomized controlled trials (RCTs)". The distinction between "evidence" ("organization of the information to inform a conclusion or judgment") and "data" ("factual information" and "one component of the research plan') are noted within the ISPOR Task Force report.

More recently, a survey of European HTA bodies revealed varying definitions of the term "real-world data", with 38 definitions identified falling into 4 categories: 1) Non-RCT data; 2) Non-interventional/controlled data; 3) Non-experimental data and 4) Other.[1] While these definitions are based primarily on research design and data sources, the ISPOR Task Force report also identified definitions based on type of outcome.[2]

Figure 1: Categorical definitions of "real-world data"



Why discuss real-world evidence?

Previous discussion supported by the IHE highlighted the fact that Canada has an abundance of real-world evidence sources but that "that accessing the data and linking it can be a challenge."[3] In a previous roundtable discussing appropriate use of routinely collected data, participants felt that both patients and health professionals should be better engaged so as to understand the potential to economic value should improve access to data and address privacy issues.

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[1] Makady et al., "What Is Real-World Data?"

[2] Garrison et al., "Using Real-World Data for Coverage and Payment Decisions."

[3] Nason and Husereau, "Roundtable on Real World Evidence System Readiness – Are We Ready to Use Routinely Collected Data to Improve Health System Performance? Summary Report – September 2014."

There was also a recognized need to improve research capacity in the area of real-world evidence, and an acknowledgment of its increasing value and importance to public payers, HTA bodies, researchers and industry (see Box 1).

Box 1: The increasing importance of real-world evidence (from Nason[4])

- **To public payers and evidence assessment agencies:** Payers must balance the need to provide improved health outcomes and access to new technologies with budgetary considerations. Clinical trials developed for regulatory purposes may be insufficient to resolve payer uncertainty.

- **To researchers:** Techniques and tools to analyze data for RWE have become increasingly widespread and accessible to researchers. Researchers are now able to answer an increasing number of important health services and policy questions without the considerable expense, length of time, and complication of conducting high-cost experimental studies.

- **To industry**: Industry views RWE as an additional opportunity to demonstrate the value of medicines, for both the patient and the health system. It may also provide new opportunities for industry to work with payers to advance novel approaches to pricing and reimbursement.

Despite more frequent discussion on this topic, the use of real-world data for payer decision-making is far from a new concept. As far back as 1997 with the 2nd edition of "Guidelines for Economic Evaluation of Pharmaceuticals" there is mention of the need for "prospective data reflecting the 'real-life' experience of the drug" and "performance of a drug in the real world" when creating estimates of effectiveness. This distinction is also made in the most current edition of the guidelines, where analysts are cautioned that results from randomized controlled trials (i.e., efficacy results) may require adjustment to estimate real-world performance (i.e., effectiveness).

What has changed is the increasing amount of available data, and the potential for use of real-world data in product-listing agreements between producers of innovation and payers. In some jurisdictions, these outcome-based performance risk-sharing agreements or conditional reimbursement schemes (CRS) have become more commonplace. However, they can be challenging to implement depending on the environment, as they require a high degree of coordination between researchers, health system service providers, administrators and industry.

[4] Ibid.

Objectives

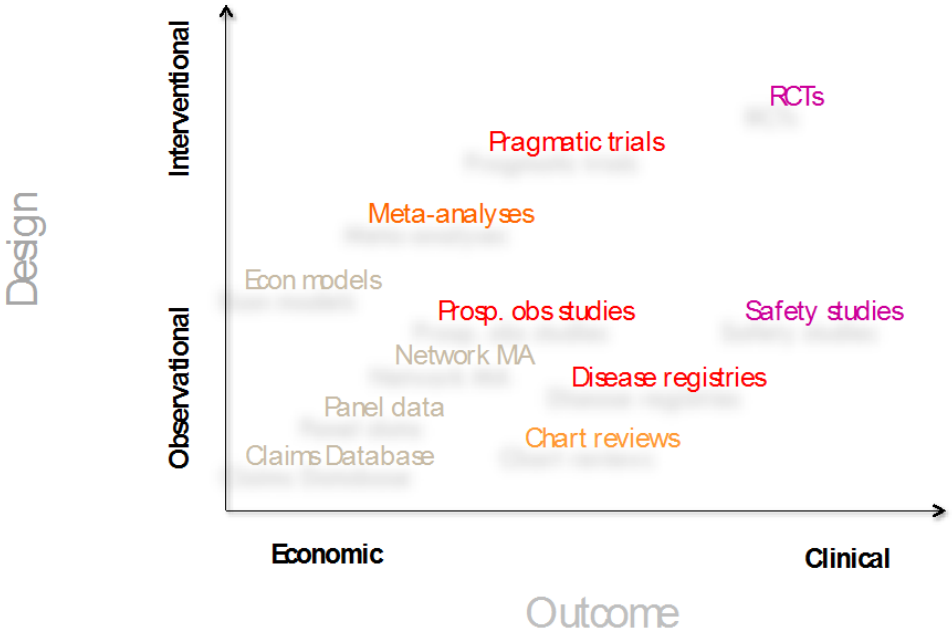
The focus of this initial discussion is to capture preferences and perceptions of the use of RWE for new medicine decisions in Canada. The use of RWE post-marketing or for conditional reimbursement is outside of the scope of this discussion. The following questions will be addressed during the discussion:

- What is the state of system readiness in the Canadian health system and current approaches to real-world evidence in drug reimbursement decisions in Canada and internationally?
- Is guidance for the use of real-world evidence in pricing and reimbursement decisions desirable and feasible?
- What approaches or next steps might be taken to developing and implementing guidance or other tools to promote the consistent use of RWE?

Policies and preferences for real-world evidence in Canada

Submissions to CADTH for new drugs or drugs with a new indication require information about efficacy/effectiveness, safety, economic and population impact as well as pricing and distribution information. A review of potential benefits and harms to patients, patients values, as well as economic and budget impact are then presented to expert committees who deliberate and create recommendations whether to reimburse, reimburse with conditions, or not reimburse. These recommendations and the information used to inform them are provided to payers who may further negotiate with public insurance providers regarding conditions to provide reimbursed access to patients. Submission packages and information presented to expert review committees require various types of analyses using different data sources and analytic methods, which often depend on what information is required (Figure 2).

Figure 2: Types of outcomes and typical study designs supporting these



CADTH Common Drug Review and pan-Canadian Oncology Drug Review submission requirements do not make evidence from randomized controlled trials mandatory – instead, applicants are asked to submit results from "pivotal" regulatory studies that in most cases are randomized trials. Both bodies additionally ask studies to be described using CONSORT guidance (which was developed for randomized trials) and ask that any new clinical information for re-submission be submitted in the form of a randomized controlled trial. It should be noted that some pivotal studies have been single arm phase 2 studies, which are basically highly controlled observational studies.

For existing and new information on safety/harm, non-randomized data is allowable. Specifically for re-submissions, CDR/pCODR guidance states "case-control or cohort studies will be accepted if randomized controlled trials are unavailable."[5]

Economic evaluations require many more pieces of information than clinical evaluations including information about natural disease progression (for model-based evaluations), societal preferences for health states (for cost-utility studies), adherence and switching rates, and resource use and costs. Current CDR/pCODR guidance does not put restrictions on where these data come from. However, the CADTH Economic Evaluation guidelines that inform this guidance do emphasize the need for approximating real-world effectiveness and costs in the analysis, including it use in model parameters and external validation, implying these data are recommended (Box 2). These preferences are similarly stated in the recently Drafted 4th edition guidelines. Similarly, no restrictions are placed on disease prevalence and incidence (epidemiological) information, although it is implied robust Canadian data would lead to more accurate estimates.

Patient value information based on solicited submission will often be based on global or national surveys conducted by patient organizations. Those submitting patient information are only asked to provide data sources and the manner in which they were achieved.

Box 2: CADTH Economic Evaluation Guidelines preferences for real-world evidence

Effectiveness, Recommendation Statement 2.63 - Where feasible in the Reference Case, incorporate "real world" factors that modify the effect of the intervention, where there are established links to important patient outcomes based on the best available evidence. These factors include patients' adherence to treatment, screening and diagnostic accuracy, and health care providers' compliance and skill. State the nature of the factor, measures used to quantify the effect, and the methods and assumptions used for modelling.

Modeling, Recommendation statement 3.6.3 – "It is preferred that the Reference Case be based on the best quantitative estimate of "real world" effectiveness, with uncertainty about the estimate handled through a sensitivity

[5] *https://www.cadth.ca/sites/default/files/pcodr/pCODR's%20Drug%20Review%20Process/pcodr-submission-guidelines.pdf* and *https://www.cadth.ca/media/cdr/process/CDR_Submission_Guidelines.pdf*

analysis. Because of good "real world" evidence is seldom available before the intervention is used in the market, analysts are encouraged to translate efficacy data into effectiveness estimates."

Current use of real-world evidence internationally

Few HTA bodies explicitly state that real-world data is preferred for evaluation through submission guidance. A recently conducted review of economic evaluation guidelines noted that many guidelines state RWE will be considered. In some cases preferences for real-world evidence is made explicit for certain pieces of evidence and in some cases, guidelines are unclear (Figure 3).

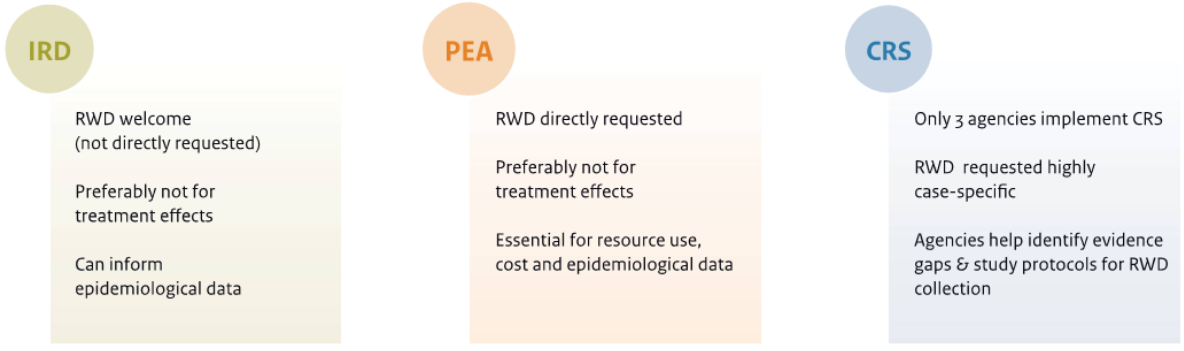
A survey of six key European HTA agencies (Sweden TLV, UK NICE, German IQWIG, France HAS, Italy AIFA and Netherlands ZIN) further indicated where and how the importance of real-world evidence is perceived by HTA bodies (Figure 4). Respondents indicated that real-world evidence may lend itself to 3 contexts in decision-making: 1) Initial reimbursement discussions (IRD); 2) Pharmacoeconomic analysis (PEA); and 3) Conditional reimbursement schemes (CRS).

Figure 3: Use of RWE in economic evaluations internationally

Country	Year	Assessing clinical effectiveness and potential risks	Inclusion as parameters in PE models	External validation of models
Americas				
Brazil	2009	▯	?	?
Canada*	2006	✪	✪	✪
Colombia	2014	?	?	?
Europe				
Baltic (Latvia, Lithuania, Estonia)	2002	?	?	?
Belgium	2015	✪	✪	?
Denmark	2008	▯	▯	?
England and Wales	2013	▯	▯	?
Finland	2015	▯	▯	?
France	2012	▯	▯	▯
Germany	2015	▯	▯	?
Ireland	2014	▯	▯	?
Norway	2012	▯	?	✪
Poland	2009	✪	✪	▯
Portugal**	1998	▯	✪	?
Scotland	2014	?	▯	?
Sweden	2003	?	?	?
The Netherlands	2006	?	▯	?
Oceania				
Australia	2015	▯	▯	▯
New Zealand	2015	▯	▯	▯

✪ = RWE is recommended
▯ = RWE will be considered
? = Position on RWE is unclear
*Updated guideline is coming out in fall/winter of 2016
**In June 2015, the National System of Health Technology Assessment was established in Portugal, and it is currently reviewing and updating the guideline
Note: Among the major European markets, only Spain and Italy lacked guidelines that are officially recognized or required by their HTA agencies. Recommendations published by experts in the field are available.

Figure 4: High-level summary of policies describing preferences and perceptions of RWE



RWD=Real world data; IRD=Initial reimbursement discussions; PEA= pharmacoeconomics analysis; CRS=conditional reimbursement schemes

Where might real-world evidence be more useful?

Although randomized clinical trials have evolved to answer questions of individual risk-benefit posed by regulators, they often create real evidence gaps for payers, who additionally have questions about population effects in the real world, including long-term safety, how dosing and compliance translate to effectiveness, use in broader populations with less monitoring, what the need is and how new medicines perform versus currently available alternatives.

Non-randomized studies using real world data provides an opportunity to answer questions payers may have including:

- Burden of illness – what is the real healthcare need in the patient population? Other populations?
- What is the real expected outcome / course of progression?
- What are patient experiences with illness? With current treatments?
- What health states and associated preferences are seen in the real world?
- What is being used in real life practice, drugs and doses for comparison?
- What endpoints are measured in real life, and how do they link with surrogate endpoints?
- What is the risk-benefit in less controlled populations?
- What utilization will occur? What does appropriate utilization look like?
- What is clinical effectiveness and resource use in real life patients?
- What is clinical effectiveness and resource use of previously unevaluated comparators?
- How is the medicine used in complex chronic conditions, with multiple therapeutic options and switches over time?
- How is the medicine use / effect changed when part of a larger complex intervention?

Questions for discussion

- How can RWE be incorporated into the current model of Canadian pricing and reimbursement process?
- Is better guidance for the use of RWE in pricing and reimbursement decisions desirable and feasible?
- How should RWE be utilized by HTA when reviewing drugs?
- If payers/HTA see value in the use of RWE, at what moment in product lifecycle this evidence should be prepared?
- Where is RWE and accompanying guidance most needed? Least needed?
- How important is to have RWE based on Canadian patients? In case of data gaps, can evidence collected in other countries be used?
- What are the biggest barriers for the Canadian payers/HTA bodies to using RWE?

- What next steps are needed to best use RWE?
    - Changes to access to data?
    - Changes to governance of available RWD?
    - Standards for data analysis and use?
    - Payer guidance?
    - Generation of a RWE framework or guidance document? If yes who should develop this guidance?
    - Payers and producers engaging in a pilot utilizing RWE?
    - What role for industry in terms of RWE generation?