

Defining decision-grade real-world evidence and its role in the Canadian context: A design sprint

Summary report of a workshop
October 21, 2018

CADTH Evidence
Driven.



Health
Canada

Santé
Canada



INSTITUTE OF
HEALTH ECONOMICS
ALBERTA CANADA

CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH

Canadian Agency for Drugs and Technologies in Health (CADTH) is an independent, not-for-profit organization responsible for providing health care decision-makers with objective evidence to help make informed decisions about the optimal use of health technologies, including: drugs; diagnostic tests; medical, dental, and surgical devices and procedures.

CANADIAN ASSOCIATION FOR POPULATION THERAPEUTICS

The Canadian Association for Population Therapeutics (CAPT) is a member-driven organization focused on the advancement of research regarding therapeutic interventions to improve the health outcomes of Canadians by bringing together diverse perspectives, facilitating open exchange of ideas and collaboration, and influencing policy and practice.

HEALTH CANADA

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

INSTITUTE OF HEALTH ECONOMICS

The Institute of Health Economics (IHE) is an independent, not-for-profit organization that performs research in health economics, synthesizes evidence in health technology assessment to assist policy making, and serves as a neutral broker to convene stakeholders from the public and private sectors to collaborate and solve key challenges in the health system.

Defining decision-grade real-world evidence and its role in the Canadian context: A design sprint

**Summary report of a workshop
October 21, 2018**

The workshop was held October 21, 2018 in Toronto, Ontario,
as a satellite to the 2018 Annual Canadian Association for Population
Therapeutics Conference.

The workshop was developed and delivered as a joint partnership between the
Canadian Agency for Drugs and Technologies in Health (CADTH);
Canadian Association for Population Therapeutics (CAPT), Health Canada, and
the Institute of Health Economics (IHE). CADTH and Health Canada
provided unrestricted grants to support the workshop;
CAPT and the IHE provided in-kind support.

The views expressed herein do not necessarily represent the official policy of
these organizations.

Acknowledgements

The members of the Steering Committee are the following:

- Dr. Tammy Clifford, Dr. Tarry Ahuja, and Peter Chinneck – Canadian Agency for Drugs and Technologies in Health
- Peter Dyrda, Dr. Allan Gillman, and Kimberly Robinson – Canadian Association for Population Therapeutics
- Rhonda Kropp and Dr. Basanti Ghosh – Health Canada

Corresponding Author

Please direct any inquiries about this report to Dan Palfrey, MPH, BSc, dpalfrey@ihe.ca.

Funding

The workshop was supported by unrestricted grants from the Canadian Agency for Drugs and Technologies in Health, and Health Canada. The views expressed herein do not necessarily represent the official policy of these organizations.

Declared Competing Interest of Authors

Competing interest is considered to be financial interest or non-financial interest, either direct or indirect, that would affect the research contained in this report or create a situation in which a person's judgement could be unduly influenced by a secondary interest, such as personal advancement.

The authors of this publication claim no competing interest.

Suggested Citation

Canadian Agency for Drugs and Technologies in Health, Canadian Association for Population Therapeutics, Health Canada, Institute of Health Economics. *Defining decision-grade real-world evidence and its role in the Canadian context: A design sprint. Summary report of a workshop.* Edmonton (AB): Institute of Health Economics; 2018.

Web Address

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license (CC BY-NC-ND), a copy of which is available at <http://creativecommons.org/licenses/by-nc-nd/4.0/>. This publication is available for free download from the IHE website at <http://www.ihe.ca>.

© Institute of Health Economics, 2018

This work may be copied or redistributed for non-commercial purposes, provided that attribution is given to the Institute of Health Economics. Modification is prohibited without the express written permission of the Institute of Health Economics.

Executive Summary

Introduction

This report follows from a real-world evidence (RWE) workshop organized in partnership between Health Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Institute of Health Economics (IHE), and the Canadian Association for Population Therapeutics (CAPT). The workshop was held on October 21, 2018 in Toronto, Ontario. This meeting was a satellite to the 2018 Annual CAPT Conference.

A total of 87 individuals registered for the event, including four speakers. Participants reflected the perspectives of regulators, public payers, clinicians/providers, academia, health technology assessment (HTA) agencies, patient advocates, and industry. The format for the day was an abbreviated design sprint.

Workshop Objectives

The objectives of the workshop were to:

1. identify the value and applications of RWE in supporting pharmaceutical regulatory and reimbursement decision-making; and
2. identify the conditions upon which RWE will be considered of sufficient quality to inform decision-making.

Design Sprint Framework

A *design sprint* is a framework to iterate through decisions and test different alternatives in a very compressed time frame. The output is typically a prototype of a product; in the case of this workshop, it was a prototype or example oncology therapeutic *life cycle evidence development plan*, with particular respect to where RWE can be useful to inform decision-making. To frame the sprint, the participants were divided into two groups, each working on a different hypothetical case study. Case studies were developed by the Steering Committee, and were intended to represent a rare and a more common condition.

Briefly, the framework for the design sprint guides sprinters to **understand** the challenge or problem from different perspectives, **define** the objectives of the sprint and the solution to be developed (the *challenge statement*), **ideate** to identify a number of different solution options, **select** the most promising option amongst the alternatives, **plan** for a means to implement the decision, and then **implement** the sprint output.

The following were the objectives of the design sprint:

- Develop a “prototype” oncology product life cycle evidence development plan, identifying the role for and quality standards required of RWE.
- Identify next steps to understand how to implement the plan, including required guidance, data considerations, and anticipated challenges.

Four 15-minute lightning talks were presented as a key contributor to the “understand” phase of the design sprint. The purpose of the talks was to identify the problem or challenge with the typical evidence base used for decision-making from different perspectives (regulatory, HTA/payer, clinician/researcher, industry), and to inform the thinking of the sprinters in terms of solutions to the challenges identified.

Design Sprint Outputs

RWE Use Cases and Priorities

The identified use cases for RWE to inform decision-making along the product life cycle were quite consistent between sprint groups. Both groups identified that RWE creates an iterative, high-priority opportunity to inform conditional reimbursement recommendations/decisions, understand product place and performance in routine clinical practice in terms of comparative safety, effectiveness, and cost-effectiveness, and expand or contract appropriate use in terms of patient profiles, indications, and place in care pathways. RWE was also consistently identified as a high-priority mechanism to assess the economic value of a therapy and adjust pricing and reimbursement recommendations and decisions as appropriate.

In terms of priorities for phase-in opportunities, both groups noted that choices made were in the context of the case study provided, and that evaluation of priority could change for different circumstances. Both groups saw a clear phase-in opportunity for RWE to inform/enable conditional reimbursement with a coverage with evidence development approach. This decision was driven by the perceived value for RWE to support this type of decision-making, and the potential for this use case to be of lower risk than one to inform a regulatory decision.

In the deliberate absence of definitions provided to characterize *quality*, it was generally defined by both groups as the degree of rigour required, or the threshold of evidence needed in order to make a decision. In the discussions, quality was viewed and considered from the perspective of the stakeholder making a decision, and the ramification(s) of the decision. The sprinters generally, and appropriately, interpreted the quality assessment as a relative exercise, and stated that lower quality requirements were not intended to express support for low-quality evidence, but rather to suggest opportunity for an increased ability to adapt interpretation to the context (including other evidence that is available).

In terms of the assessment of the relative quality required for RWE to be *decision-grade*, the bias of the sprinters was towards the highest quality being required when used to support regulatory decisions. There appeared to be greater comfort with a lower degree of required quality when RWE is used to support HTA/reimbursement decision-making, and where there is greater opportunity for RWE to serve as one input amongst others that are included in the total body of evidence informing a decision.

A conclusion from the quality discussion is that, in developing a quality framework, we should articulate an ideal future state reflective of the highest quality possible, but also consider how a framework can be practically implemented in the near term to support RWE generation and utilization for important decisions where there is uncertainty. In other words, a developed framework should have enough rigour and precision to be helpful, but also enough flexibility that it is realistic, implementable, and can be accepted and used in a case-dependent, context-specific manner in light of the opportunities and limitations that we currently have.

RWE Quality Standards

Sprinters across the two groups were challenged to define specific standards for RWE quality. Quite reasonably, the sprinters consistently identified that the value and use of RWE will be highly context-dependent, and, as such, there is a need to consider each opportunity for RWE on a case-by-case basis. That said, a number of themes emerged from both sprint group discussions that are

instructive to support the increased phasing-in of RWE along the decision continuum going forward. The following key themes were uncovered during the discussions.

The process followed is as important as any defined standards

Given that RWE generation and utilization is very context-specific, it is challenging to articulate prescriptive guidance that is intended to be closely followed. Rather, it is advisable to articulate a good process to follow, that leads to the highest quality RWE that will be of the greatest value to decision-makers.

Look to good research practices currently in use for guidance on RWE

There may not be a need to identify specific, unique approaches for RWE in guidance that is produced, rather well-accepted practices (for example, representativeness of patient populations studied, appropriate sample sizes) from existing fields such as epidemiology and statistics can serve to shape an acceptable approach to RWE.

Develop a framework to identify the context, and to guide key aspects of RWE generation

A framework incorporating well-defined acceptable practices from relevant fields that defines a structured decision-making process for RWE generation will be useful to identify conditions of acceptability of RWE to decision-makers. We should learn and align with other jurisdictions completing similar work, such as the Duke-Margolis RWE Collaborative in the United States which structures RWE considerations around the regulatory and clinical context for the decision problem and offers considerations for data (for example, completeness, reliability, validity) and methods (study design and credibility), which collectively leads to fit-for-purpose RWE.

Involve key stakeholders and gain agreement at the outset

Given the need for judgement and good planning, and in the absence of implementable guidance articulating clear standards intended to be closely followed, stakeholder engagement and participation is critical. An inclusive and collaborative approach will permit those who sponsor, generate, and use RWE to have a voice when following a structured RWE development process, reducing uncertainty, ensuring clarity on the decision problem to be informed, and increasing the expected value of the RWE. How and what decisions will be made on the basis of the RWE generated should be clear and agreed to at the outset (for example, a priori establishment of metrics to be considered, thresholds, how they may be considered in context of other evidence, and what decisions they will drive).

Trust is key

Trust between stakeholders is critical for successful collaboration. Trust depends on the distribution of risk, and less risk for each stakeholder can result in increased trust. Risk is proportional to uncertainty; with less uncertainty comes less risk and more trust. A clear, inclusive, structured process to develop and use RWE will decrease uncertainty, reduce risk, and create trust.

We can learn by doing

As we gain experience with RWE to support specific decision problems, over time we will learn and be in a better position to recommend a more consistent and standard approach to achieving quality. This will support scale of RWE and less resource-intensive approaches to RWE generation and utilization.

Start with something simple

There is opportunity currently to start with some of the priority use cases identified at this workshop and phase-in the use of RWE to support decision-making. We can start with something that is relatively more simple, of lower risk in terms of decision consequence, learn, achieve some early wins, and gain some trust. To do this we need to be equally comfortable with being uncomfortable, and be comfortable with the discomfort.

RWE Implementation Considerations

The last section of the design sprint brought both sprint groups together for a discussion of life cycle evidence development plan implementation considerations. The group reinforced that detailed, prescriptive guidance is not practical or feasible. Rather, guidance will need to be at a principle or factors/considerations level in order to be implementable, should ideally be aligned with emerging international standards to inform a Canadian approach, and should be considered in terms of a planned series of updates over time as we learn by doing. It was recommended that the development of guidance occur through a very collaborative approach, with all stakeholders participating. It was noted that guidance should not just be considered for the biopharmaceutical industry, but also for the research community, data custodians, and those who provide the technical and infrastructure support to process and analyze data. In addition to considerations for RWE data sources and study design, it was suggested that prioritization and sharing of which areas of focus or policy questions are considered to be most important by Health Canada, HTA agencies, and payers would be helpful to focus the initial efforts of industry and the research community.

Moving forward, a standing, sustainable forum for multi-stakeholder dialogue, similar to initiatives in Europe and the United States, was encouraged. The group reinforced that we currently have the data and technical capabilities/methods to produce quality RWE, and the biggest challenge is aligning stakeholders and building trust. It was recommended that we learn from previous experience, such as with conditional reimbursement and risk-sharing agreements, and understand how to overcome barriers that have been encountered (for example, data ownership, distribution of risk, legal/ethical considerations) in order to accelerate the phasing-in of a greater role for RWE to inform decision-making.

Concluding Comments

The design sprint workshop represented a good start in terms of a broad group of stakeholders coming together to discuss, in a concrete manner, complex and challenging issues related to an increased role for RWE to inform decision-making across the product life cycle. A rich and productive discussion took place, with stakeholders from different perspectives engaging and sharing experiences and considerations. Clearly this workshop was a good start; however, there is much more to do to articulate, implement, and monitor a thoughtful and sustainable Canadian approach and guidance for phasing-in a more meaningful role for RWE. The level of interest and engagement at this workshop suggests that the stakeholder community is prepared and willing to continuously be engaged to move the conversation forward, and to participate in similar future forums and working groups to support Canada to better utilize RWE to inform important decision-making across the pharmaceutical product life cycle, with the objective to improve appropriate access to necessary therapies for Canadians.

Abbreviations

All abbreviations that have been used in this report are listed here unless the abbreviation is well known, has been used only once, or has been used only in tables or appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

CCO	Cancer Care Ontario
HTA	health technology assessment
RCT	randomized controlled trial
RWD	real-world data
RWE	real-world evidence

Table of Contents

Acknowledgements.....	i
Executive Summary	ii
Abbreviations	vi
1. Introduction	1
1.1. Workshop Overview.....	1
1.2. Objectives and Agenda	1
1.3. Design Sprint Framework	2
<i>Figure 1: Design sprint framework.....</i>	<i>2</i>
2. Summary of Lightning Talks	3
2.1. Regulatory Perspective.....	3
2.2. Health Technology Assessment Perspective.....	5
2.3. Clinician/Researcher Perspective	6
2.4. Industry Perspective	8
3. Summary of Design Sprint	10
3.1. Overview.....	10
3.2. Design Sprint Outputs	12
3.2.1. Case Study 1	12
<i>Figure 2: Case Study 1 – life cycle evidence development plan</i>	<i>12</i>
<i>Table 1: Case Study 1 – summary RWE use cases and characterization</i>	<i>12</i>
3.2.2. Case Study 2	13
<i>Figure 3: Case Study 2 – life cycle evidence development plan</i>	<i>14</i>
<i>Table 2: Case Study 2 – summary RWE use cases and characterization</i>	<i>14</i>
3.2.3. RWE Use Cases and Priorities	15
3.3. RWE Quality Standards.....	16
3.4. RWE Implementation Considerations	17
4. Concluding Comments	18
Appendix A: Workshop Program	20
Appendix B: Workshop Registrant Affiliations.....	22
Appendix C: Design Sprint Case Studies	23

1. Introduction

1.1. Workshop Overview

This report follows from a real-world evidence (RWE) workshop organized in partnership between Health Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Institute of Health Economics (IHE), and the Canadian Association for Population Therapeutics (CAPT). The workshop was held on October 21, 2018 in Toronto, Ontario. This meeting was a satellite to the 2018 Annual CAPT Conference.

A total of 87 individuals registered for the event, including four speakers. Participants reflected the perspectives of regulators, public payers, clinicians/providers, academia, health technology assessment (HTA) agencies, patient advocates, and industry. The format for the day was an abbreviated design sprint (please refer to section 1.3 for further information).

For a copy of the program, including the agenda and biographies of the speakers, please see Appendix A; for a list of registrant affiliations, please see Appendix B; for the case studies used during the workshop, please see Appendix C.

1.2. Objectives and Agenda

The objectives of the workshop were to:

1. identify the value and applications of RWE in supporting pharmaceutical regulatory and reimbursement decision-making; and
2. identify the conditions upon which RWE will be considered of sufficient quality to inform decision-making.

The agenda for the workshop is below.

Time	Topic	Presenter/Facilitator
9:00-9:15	Welcome & Design Sprint Overview	Allan Gillman
9:15-10:15	Lightning Talks	Tammy Clifford, Rhonda Kropp, Kelvin Chan, Michael Duong
10:15-10:30	Break	
10:30-10:45	Design Challenge Statement & Case Study Presentation	Dan Palfrey
10:45-12:45	Identification of Applications of RWE (Breakout Rooms – Sprint 1)	Kimberly Robinson, Peter Dryda
12:45-1:30	Lunch	
1:30-2:30	Identification of “Decision-Grade” Quality Standards (Breakout Rooms – Sprint 2)	Kimberly Robinson, Peter Dryda
2:30-2:45	Break	
2:45-3:45	Identification of Implementation Considerations	Dan Palfrey
3:45-4:00	Wrap-Up & Adjourn	Tammy Clifford, Rhonda Kropp

The following definitions were used to guide the workshop:ⁱ

- *Real-world data* (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- *Real-world evidence* (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

1.3. Design Sprint Framework

A *design sprint*, modelled after work at IDEO, Google Ventures, and the d.school at Stanford, is a framework to iterate through decisions and test different alternatives in a very compressed time frame. The output is typically a prototype of a product; in the case of this workshop, it was a prototype or example oncology therapeutic *life cycle evidence development plan*, with particular respect to where RWE can be useful to inform decision-making. To frame the sprint, the participants were divided into two groups, each working on a different hypothetical case study. Case studies were developed by the Steering Committee, and were intended to represent a rare and a more common condition.

The participants were defined either as *sprinters*, meaning those that completed the design sprint, or *observers*. The latter type of participant was identified due to a need to limit the size of the group of sprinters. Each table of six to eight sprinters worked as a group to contribute to the development of the output plan. Sprinters were seated at tables that reflected the different perspectives of meeting participants in order to encourage robust discussion. Four speakers initiated the sprint with 15-minute lightning talks, with the objectives to share a particular perspective (regulatory, HTA, clinician/researcher, industry) on the challenges with the typical evidence base upon which decisions are made, and to inform the thinking of the sprinters in terms of solutions to the challenges identified. Figure 1 below presents the framework of a design sprint.

FIGURE 1: Design sprint framework



Briefly, the framework for the design sprint guides sprinters to **understand** the challenge or problem from different perspectives, **define** the objectives of the sprint and the solution to be

ⁱ US Food and Drug Administration (FDA). *Use of real-world evidence to support regulatory decision-making for medical devices: Guidance for industry and Food and Drug Administration Staff*. FDA: 2017. Available from: <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>.

developed (the *challenge statement*), **ideate** to identify a number of different solution options, **select** the most promising option amongst the alternatives, **plan** for a means to implement the decision, and then **implement** the sprint output.

The following were the objectives of the design sprint:

- Develop a “prototype” oncology product life cycle evidence development plan, identifying the role for and quality standards required of RWE.
- Identify next steps to understand how to implement the plan, including required guidance, data considerations, and anticipated challenges.

The case studies used to frame the design sprint are summarized in section 3.1. For a full review of the cases and guiding questions, please refer to Appendix C.

2. Summary of Lightning Talks

Four 15-minute lightning talks were presented as a key contributor to the “understand” phase of the design sprint. The purpose of the talks was to identify the problem or challenge with the typical evidence base used for decision-making from different perspectives, and to inform the thinking of the sprinters in terms of solutions to the challenges identified.

2.1. Regulatory Perspective

Rhonda Kropp – Health Canada

At the January 2016 Health Ministers meeting, there was a commitment made to improve the affordability, accessibility, and appropriate use of therapeutic products. As part of this, Health Canada’s Health Products and Food Branch launched an initiative called *Regulatory Review of Drugs and Devices* (R2D2). Of the 15 projects under R2D2, there are two focused on RWE, one each for drugs and devices. The goal of the projects are to improve Canada’s ability to assess and monitor product safety and effectiveness across the life cycle, by optimizing the use of RWE. The word *optimize* is used deliberately, as Health Canada currently uses RWE to inform some decisions, however in very limited areas, for example where an RCT is infeasible or unethical. Health Canada would like to understand how to use RWE more broadly across the pharmaceutical life cycle.

The desired end state from Health Canada’s perspective is for RWE to be used appropriately across the entire product life cycle, improving timely access to health products for Canadians. However, evidence that is submitted must be of sufficient quality to be used for decision-making purposes. To achieve this, all stakeholders must work together to jointly define what will be considered *quality* RWE. Optimizing RWE use across the life cycle in no way means Health Canada will lower its regulatory decision-making bar; rather that the bar will be adapted to fit the circumstances.

There is also interest in ensuring that the assessment of quality of evidence is, where possible, aligned with domestic (for example, HTA groups) and international partners. To achieve this, initiatives to inform Health Canada in this area will be done in partnership with other organizations and stakeholders. Additionally, assessment of sufficiency of evidence to support a decision will, by necessity, be a case-by-case decision, and Health Canada and industry partners will work collaboratively for a given submission to determine the potential use of RWE for a given decision problem.

Moving forward, Health Canada will publish a strategy outlining how it will optimize the use of RWD/RWE across the product life cycle. The strategy will include guidance for industry and data partners that will identify a transparent approach to assessing quality of evidence that will be used in a consistent manner by Health Canada.

Health Canada does not have interest in doing pilot projects, which imply a test prior to moving forward with the approach. Rather, the regulator has made a decision to move forward with increased appropriate use of RWE along the pharmaceutical product life cycle, and is interested in understanding where early phase-in opportunities exist. Initial thoughts suggest this opportunity exists most obviously in oncology, as well as for rare conditions where more expensive medications represent a treatment option.

Health Canada has interest and is committed to working with partners to optimize data availability. There are a lot of data currently available in Canada that can be utilized, as well as some obvious gaps that we can work together to fill. The Drug Safety and Effectiveness Network (DSEN) is a significantly under-utilized resource, with much promise to support RWE, and it is anticipated that there will be much greater use of DSEN in the future to answer priority research questions.

This workshop provides an excellent opportunity for partners that generate and use RWE to discuss key challenges and opportunities in a concrete way (and move beyond talking and begin doing). Health Canada understands that the path forward needs to be a collaborative one, involving and consulting with key partners and stakeholders, and aligning as much as possible with other organizations that make or support decisions that can be informed by RWE. Today's workshop is not an isolated opportunity for partnership on this topic, it is a first step; success on this journey will require many partners working together, understanding each other's needs and how we can support one another with the aim of optimizing access to safe and effective therapeutic products in Canada. The planned approach for Health Canada is presented below.

Planned Approach

Moving forward, HC will publish a strategy outlining how we will optimize the use of RWD/RWE across the product life cycle. Snapshot of the approach....

1. Developing Guidance for Industry and Data Partners
 - Publishing principles and guidance for industry and data partners on the key data elements needed for decision points across the product life cycle and how HC and Industry can work together to optimize RWE use early on in submission discussions
2. Developing and Implementing a Transparent Approach to Assessing Quality of Evidence
 - Documenting the approach to assessing quality of evidence submitted across the life cycle.
 - Aim is to support data producers in collecting the right data of sufficient quality to inform regulatory decision making
3. A Phased Approach to Implementation
 - Health Canada already accepts RWE as part of submissions across the life cycle, however, with the Guidance and Quality of Evidence (QoE) approach clarified, we will work with willing partners to phase in deliberate use of RWE starting with product lines for which use of RWE provides clear value-add to the health system and to Canadians. Lessons learned will be used to optimize the approach for future phases.
4. Working with Partners to Optimize Data Availability
 - Collaborating with partners to support the development/sharing/optimization of sources with greatest Return on Investment (RoI) for Canadians.
 - Monitoring the safety and effectiveness of medical devices on the market requires data, both to identify signals and proactively assess for potential issues
 - Regulatory and non-regulatory solutions will be assessed

2.2. Health Technology Assessment Perspective

Dr. Tammy Cliffordⁱⁱ – CADTH

CADTH's three year strategic plan came into effect in April of this year, and includes a transformation from CADTH serving as an HTA body, to one that supports the system more broadly in terms of health technology management (HTM). This suggests a much stronger life cycle approach to HTA to be taken by the agency, both for devices and pharmaceuticals. This approach will align review processes with federal, provincial, and territorial priorities throughout all phases of the technology life cycle, and CADTH will be working very closely with partners in order to achieve this.

The strategic plan is reflected in the current year CADTH business plan, where there is an explicit priority for the agency to establish processes to enable more informed decision-making throughout the technology life cycle. This work will be completed in collaboration and alignment with key partners, including Health Canada, the Patented Medicines Pricing Review Board, the pan-Canadian Pharmaceutical Alliance, and the Canadian Association of Provincial Cancer Agencies. The overarching goal is to support greater technology accessibility, affordability, and appropriate use. CADTH will engage with key stakeholders to develop a pan-Canadian framework for the collection of RWD on technology use and outcomes, and a revised framework for technology reassessment, intended to enable decisions informed by more relevant, context-specific RWE.

The revised reassessment framework will utilize the existing reassessment pathways at CADTH, and, where reassessment requires further input, RWE is expected to play a key role. Currently, there is no pan-Canadian process that “requires” a listed drug to be reassessed at a future (pre-planned) date. To support more systematic reassessment, conditional reimbursement agreements that include mandatory RWE development as a condition of reimbursement could play a role. CADTH currently cannot include reimbursement recommendations conditional upon reassessment within a reassessment framework until major implementation challenges are addressed, including the lack of:

- leverage to force compliance with reassessment (that is, to compel RWE development);
- detailed guidance to support RWE data and analysis approaches; and
- clarity on who is responsible for funding RWE generation.

CADTH currently utilizes RWE during its review of technology, as different types of data help to answer different types of questions. For example, the pan-Canadian Oncology Drug Review's Expert Committee (pERC) has previously issued conditional coverage recommendations. However, the required approach is not as consistent or transparent as it should be, and there is a need for greater clarity for both those that generate and submit RWE, but also for staff reviewers to ensure a consistent approach that is well understood and replicable. RWE will not replace the need for randomized controlled trials (RCTs); however, it is desired that it is available for (re)assessments when needed, and is of sufficient quality. A desired approach for CADTH, ideally aligned with Health Canada, is to provide manufacturers with early scientific advice on both pre- and post-market studies and analyses, including those that use RWD to generate RWE. The planned approach for CADTH is presented below.

ⁱⁱ With comments from Dr. Trevor Richter.

Planned Approach

2018-19 Talking: Exploration, Consultation & Development of Plan (and more consultation)

Today's workshop is an essential element – thank you!

- What already exists to better enable the use of RWE in life-cycle HTA?
- What can be done in the short-, medium- and long-term?
- What (else) needs to be done to enable an efficient evidence ecosystem
- How do we manage the risks associated with the use of RWE to inform decision-making?
- What do you need from CADTH vis-a-vis RWE?

2019-20 Doing: Implementation – phased approach

- Guidance to provide transparency & consistency in approach
- Continued efforts to optimize alignment across health system nodes (e.g., NOC/c with RWE requirement could align with conditional coverage recommendation)
- Work with data partners to optimize data availability
- CQI in support of a learning health system

2.3. Clinician/Researcher Perspective

Dr. Kelvin Chan – Sunnybrook Odette Cancer Center/University of Toronto

Foundational RWE work has taken place in the past, in particular by Cancer Care Ontario (CCO), that can help guide greater clarity on the role for RWE going forward. For example, the first prospectively planned life cycle population-based RWE study was a collaboration between the Ontario Ministry of Health and Long-Term Care and CCO. It was initiated in 2010 to complete a life cycle reassessment analysis of the oncology therapeutic product azacitidine, addressing implementation concerns with pre-planned prospective collection of RWD to generate RWE to inform reassessment. Additionally, in 2007, CCO launched an initiative entitled *Your Symptoms Matter*, which is a population-wide longitudinal collection of patient reported outcome measures (using the Edmonton Symptom Assessment Scale). This wealth of data is now available to support the conduct of comparative real-world outcomes analyses, for example a 2016 study examining pancreatic cancer patient symptom change over time across cancer drugs.

A role for RWE has been formalized in the recommendations and planning of key organizations in Ontario. In 2015, the Cancer Quality Council of Ontario identified a number of recommendations relative to drug funding accountability and sustainability, and two of them relate to RWE:

- RWE should be used to inform and monitor the effects of funding decisions.
- A consistent process to use RWE to inform disinvestment or reinvestment, as well as re-negotiation of prices, should be explored.

CCO's *Ontario Cancer Plan IV* has a stated goal that, by 2019, “[d]rugs funded through the Provincial Drug Reimbursement Program will be evaluated for the greatest benefit to patients and impact on healthcare resources.”ⁱⁱⁱ

There is interest in examining data readiness in Ontario as well as other provinces. With the support of the Canadian Partnership Against Cancer, in collaboration with the Canadian Association of Provincial Cancer Agencies and the Canadian Centre for Applied Research in Cancer Control, a three-province collaboration (British Columbia, Ontario, and Saskatchewan) has been formed to conduct a comparative analysis of the budget impact, safety, effectiveness, and cost-effectiveness of bevacizumab, a drug for metastatic colorectal cancer. The final report is expected in November 2018.

This previous work has been leveraged to successfully secure funding from the Canadian Institutes of Health Research for the development of a framework to support the incorporation of RWE into Canadian cancer drug funding decisions in a consistent and integrated manner. This multi-year, multi-stakeholder initiative is called the *Canadian Real World Evidence for Value of Cancer Drugs Collaboration* (CanREValue). The framework is intended to enable reassessment of cancer drugs by HTA bodies, help payers to refine funding decisions, and inform any renegotiations or reinvestments. The project is in its second year, and thus far an environment scan has been conducted and a qualitative study has been completed. The environmental scan has identified that there is no universal definition of RWE and RWD, there are multiple data sources for RWD and study designs for RWE that are perspective-dependent, and various stakeholders can benefit from the application of RWE/RWD along the drug life cycle. The qualitative study examined the views of stakeholders from different perspectives, and identified that increased use of RWE along the product life cycle requires a paradigm shift, there is uncertainty about the state and readiness of the data, and there is a need to build capacity and enable collaboration amongst stakeholders and organizations.

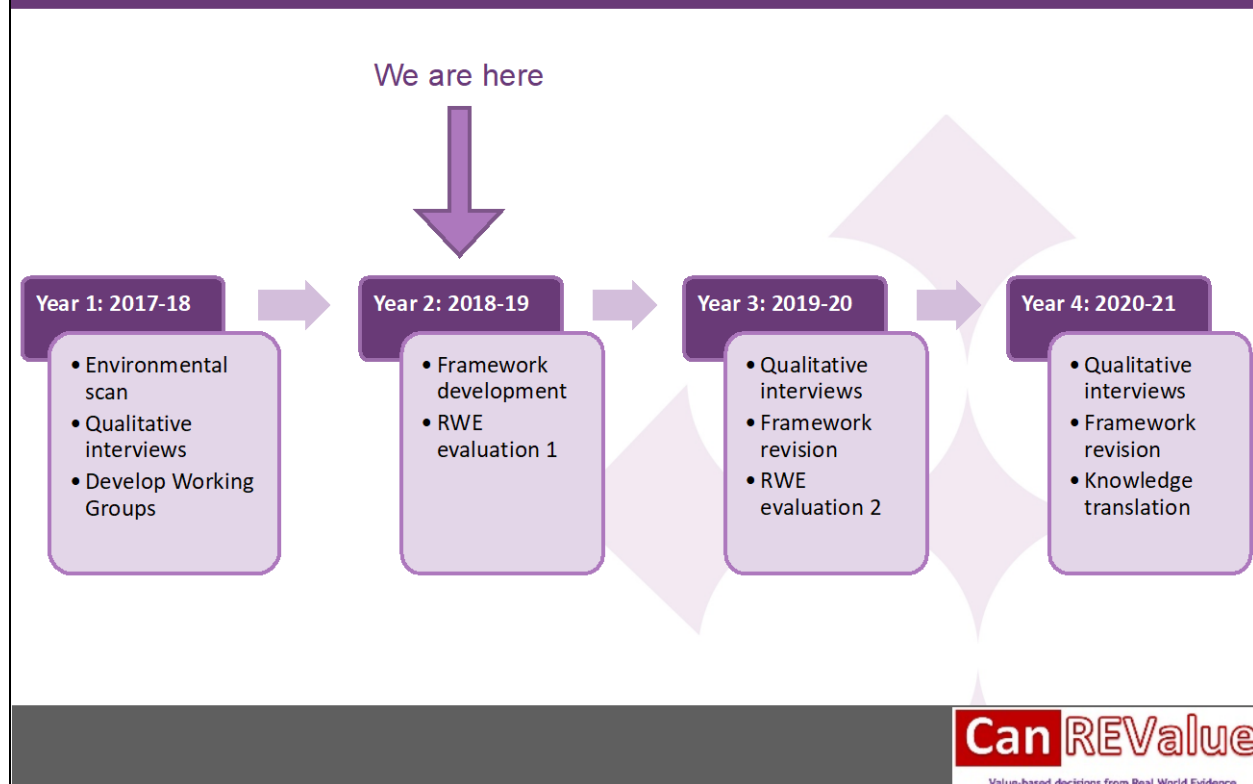
Five working groups have been established to support the development of the CanREValue framework:

- **RWE Methods:** recommend methods to analyze RWD with methodological rigour
- **RWE Data:** identify strategies for data access across provinces and harmonize data elements relevant for RWE studies
- **RWE Planning and Drug Selection:** develop criteria to identify potential drug indication candidates for real-world evaluation and establish provincial infrastructure for RWE
- **RWE Uptake and Reassessment:** develop strategies for implementing RWE results for HTA reassessment and policy decision-making
- **Stakeholder Engagement:** ensure appropriate input from key stakeholders throughout the framework development

The timelines and next steps for this initiative are presented below.

ⁱⁱⁱ Cancer Care Ontario (CCO). *Ontario Cancer Plan IV 2015-2019*. Available from: <https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOOntarioCancerPlan4.pdf>.

Timeline & Next Steps



2.4. Industry Perspective

Dr. Michael Duong – Hoffman La Roche Ltd.

This workshop, as an initial first step in bringing together key stakeholders in a practical manner to discuss how to increase the use and value of RWE to the health system, is very encouraging. It represents a pivotal opportunity for all stakeholders to engage on a topic of paramount importance and, together, take a giant leap forward in the application of RWD/RWE for healthcare decision-making. We should challenge our thinking and move the discussion beyond just optimizing the use of RWE, to maximizing the use of RWE across the life cycle of a drug.

There are challenges with the current evidence base that we use to make decisions, creating opportunity for RWE to be useful. There are clear situations within a product development program where RCT evidence is not ideal or not available, for example for personalized healthcare solutions, in rare diseases, and in areas of unmet need where we do not have a control group. However, a challenge with obtaining access to currently available RWD makes it difficult and/or inefficient to generate RWE to support decision-making.

There are many opportunities where RWE can be used to usefully inform decision-making along the product life cycle, including:

- research planning (for example, patient selection, endpoint selection) and supporting new or expanded indications and populations;
- informing disease characteristics and innovative reimbursement models, and validating surrogate endpoints; and
- supporting regulatory actions (for example, safety analyses, expanded labels) and health technology management, and optimizing reimbursement criteria.

Industry believes, as do other stakeholders, that it is possible to generate high quality RWE that is “regulatory-grade.” This represents a very significant opportunity to improve our understanding and decision-making, as the vast majority of data regarding outcomes achieved with therapy is collected in real-world settings outside of RCTs. The development of frameworks and guidance, with full transparency, to structure and inform both where RWE will be impactful in decision-making and the quality standards required, is important for industry in order to allocate resources to the generation of RWE. International groups and consortia are working on frameworks and quality standards, and is important for Canada to consider international efforts and align as appropriate. It is critical to recognize that, while healthcare decisions are local, the pharmaceutical industry in Canada consists largely of global organizations. Global clinical development programs must reflect the needs and requirements of many jurisdictions, and Canada should be deliberate in ensuring that we do not have misalignment between local and international requirements. Frameworks and guidance should be co-developed by all stakeholders (regulatory, HTA, payers, industry, patients, etc.), and should be implemented and iterated with a bias towards learning-by-doing, and ensuring that frameworks keep up with the pace of change in the environment.

In terms of how we can consider RWE quality, the evidentiary bar required to make healthcare decisions should reflect the variability of factors that influence a drug or therapeutic area (for example, ethical considerations, disease characteristics), and be as flexible as appropriate. Quality in RWE generation and utilization can be achieved through clarity, consistency, and transparency in the decision-making process. We need to set a high but achievable bar, in order to establish the required evidence to provide the most appropriate access for patients to needed therapies.

Solutions Requested From Sprinters

Things to consider for the sprinters as you're coming up with solutions

- While healthcare decisions are local, the industry is international
 - Eg. Our clinical development programs will reflect the needs and requirements of other jurisdictions (FDA, EMA) and we cannot have misalignment between local needs and international needs
- Technology and innovation in data science is accelerating at a breakneck pace
 - Many things we thought that we could not do with data in the past are becoming reality in the present

3. Summary of Design Sprint

3.1. Overview

The challenge statement shared with the sprinters was to develop a “prototype” oncology therapeutic life cycle evidence development plan that identified the:

- role for RWE at key points in the product life cycle;
- quality required; and
- implementation considerations.

The sprinters were divided into two groups, each working on a different case study. The case studies used to frame the design sprint are summarized below; one of the case studies identified an oncology therapeutic for a rare condition (Case 1), and the other identified an oncology therapeutic for a more common condition (Case 2). For a full review of the case studies and guiding questions, please refer to Appendix C.

Case Study Presentation – Case 1

- Rare cancer that primarily affects the nervous system in infants.
- Significant morbidity and early mortality.
- Drug B currently available.
- Drug X submitted to HC for authorization:
 - 22 symptomatic patients evaluated in non-randomized, single-arm dose escalation study relative to 42 untreated patients from a natural history cohort.
 - Drug X-treated patients demonstrated fewer declines in walking ability compared to untreated patients in the natural history cohort.
 - Safety evaluated in 24 patients who received at least one dose of Drug X in the clinical study.
- Comparative effectiveness with Drug B has not yet been assessed.

Case Study Presentation – Case 2

- Drug Z, based upon combination therapy RCT data, indicated for use as an adjuvant treatment for prostate cancer in addition to Androgen Deprivation Therapy (ADT).
- ADT associated with increased risk of fracture.
- Trend observed towards reduced fracture risk with Drug Z in combination therapy with ADT.
- Trials ongoing for the potential use of Drug Z as monotherapy in patients with increased risk of fracture, and those intolerant to ADT, results not expected for 2 years.

3.2. Design Sprint Outputs

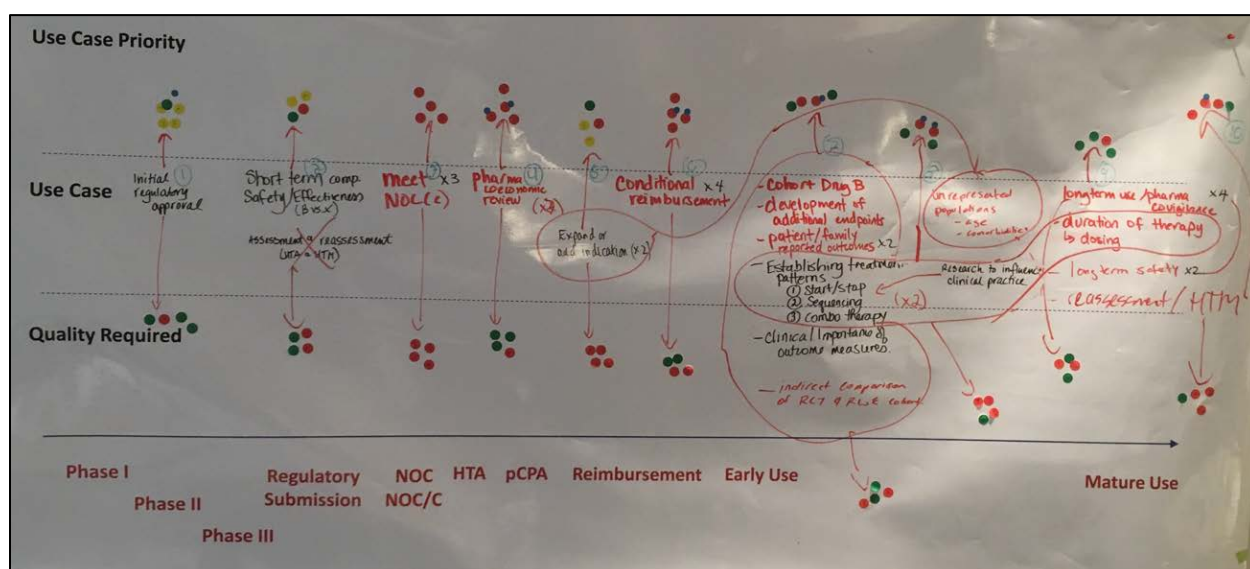
The sprinters worked within a two-hour timeframe to develop the life cycle evidence development plan, with reference to a case study, with the goals of identifying:

- key uses cases where RWE can add value;
- use case priority;
- the relative quality required; and
- recommended first-mover phase-in opportunities.

3.2.1. Case Study 1

The life cycle evidence development plan as prepared by the sprinters is presented in Figure 2 below.

FIGURE 2: Case Study 1 – life cycle evidence development plan



Colour legend: red = high; green = medium; yellow = low; blue = phase-in opportunity

The following table summarizes the output from this segment of the design sprint.

TABLE 1: Case Study 1 – summary RWE use cases and characterization

Use case	Point in life cycle	Use case priority	Phase-in opportunity	Quality required
Inform initial NOC	Clinical development program	Low – may be useful if there is data from other countries; however, if a current treatment is available, there is less urgency to use RWE	Y – this represents a lower risk opportunity to build a framework for how RWE can be used for NOC	Medium

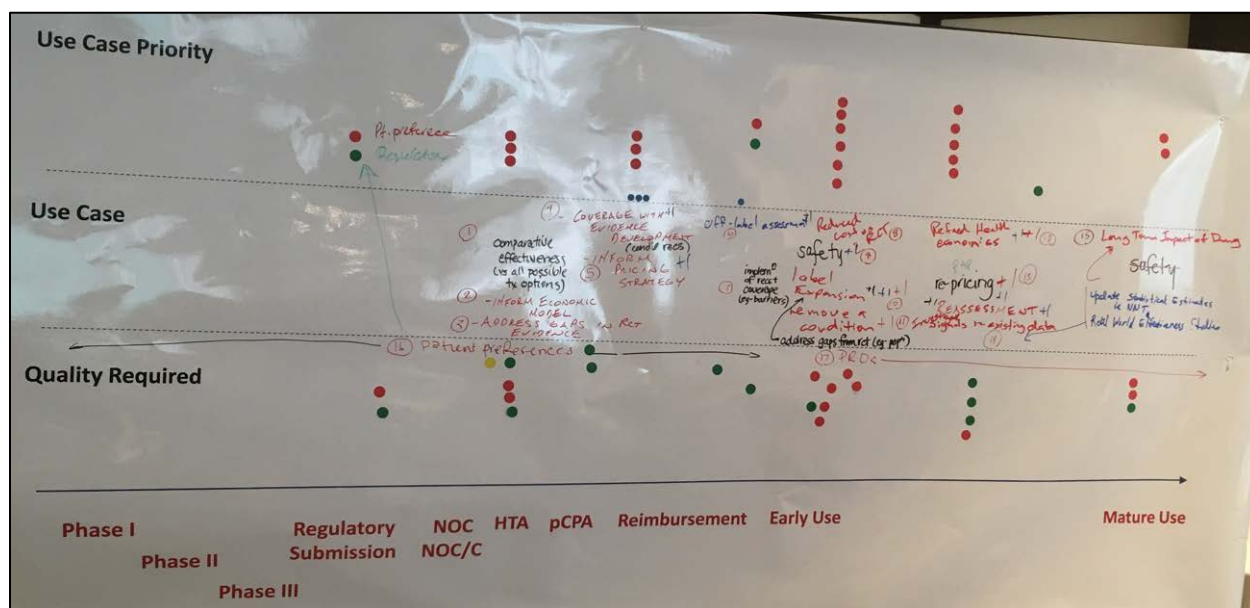
Use case	Point in life cycle	Use case priority	Phase-in opportunity	Quality required
Describe short-term comparative safety and effectiveness	Regulatory submission	Medium		Medium/High
Establish requirements to satisfy conditions of NOC/c	Regulatory decision	High – there is no comparative trial at NOC so RWE useful		High
Inform pharmacoeconomic review	HTA review	High – there is high uncertainty, assumptions can be monitored with RWE	Y,Y	Medium
Support indication addition or expansion, or establish requirements to inform label change, including confirmation of safety and effectiveness in unrepresented populations in trials (older children, co-morbidities, etc.)	Reimbursement decision	Low/Medium – particularly valuable in relation to age of approved patient population (to avoid inappropriate restriction of access), and if other similar therapies have a more broad indication, but lower priority for this case given other higher priority requirements to support the initial indication		High
Inform/enable conditional reimbursement	Reimbursement decision	High	Y,Y	Medium/High
Determine comparative outcomes observed (including patient reported, and other clinically important outcomes additional to those studied in trials)	Early use	Medium/High – the outcome studied in the trial may not be the most clinically relevant to evaluate long-term outcomes	Y	Medium/High
Establish place in care pathway and drug optimization (dose, duration, combination therapy), considering treatment patterns	Early use	Medium/High – very small population of prescribers/patients so in this case less important	Y,Y	High
Inform long-term pharmacovigilance (safety, effectiveness, cost-effectiveness)	Mature use	Medium – given a pediatric population and the observed adverse reactions there is a need to monitor		Medium/High
Inform HTA/payer reassessment (including of other drugs in care pathway)	Mature use	High – required to ensure value is being realized from investment	Y	High

NOC: Notice of Compliance; NOC/c: Notice of Compliance with conditions; Y: yes

3.2.2. Case Study 2

The life cycle evidence development plan as prepared by the sprinters is presented in Figure 3 below.

FIGURE 3: Case Study 2 – life cycle evidence development plan



Colour legend: red = high; green = medium; yellow = low; blue = phase-in opportunity

The following table summarizes the output from this segment of the design sprint.

TABLE 2: Case Study 2 – summary RWE use cases and characterization

Use case	Point in life cycle	Use case priority	Phase-in opportunity	Quality required
Address gaps in RCT evidence/comparative effectiveness analysis (examining all treatment options, even beyond medications, which may not be those captured in the clinical trials, including capturing and comparing to patient preferences and reported outcomes)	HTA review	High		Medium/High – any information on patient preferences and or outcomes is valuable and can be worked into analyses
Inform economic models	HTA review			
Inform/enable conditional reimbursement/coverage with evidence development/initial pricing	pCPA/ Reimbursement decision	High – including the ability to permit pay-for-performance agreements	Y,Y,Y	
Assess off-label use, effectiveness, and safety, use in new populations not studied, and support indication addition or expansion	Early use		Y	High – particularly when there is a requested label change

Use case	Point in life cycle	Use case priority	Phase-in opportunity	Quality required
Inform on the implementation of reimbursement decisions (identification of barriers to patients obtaining access when reimbursement is available)	Early use			
Inform on experience with product in terms of observed safety and effectiveness in clinical practice, including specific examination of safety signals from the clinical program	Early use	High – work here may be foundational to support other use cases, and obtaining the patient perspective is critical		High
Generate evidence to remove a condition of NOC	Early use			High
Inform HTA/payer reassessment/re-pricing (including supportive information on fracture risk reduction)	Mature use	High – follows from conditional reimbursement use case		Medium/High – potential to impact patient access so need rigour
Inform long-term pharmacovigilance, including capturing and comparing to patient reported preferences and outcomes	Mature use	High		Medium – information can be triangulated so does not have the same influence as an RCT/pivotal trial

NOC: Notice of Compliance; pCPA: pan-Canadian Pharmaceutical Alliance; Y: yes

3.2.3. RWE Use Cases and Priorities

The identified use cases for RWE to inform decision-making along the product life cycle were quite consistent between sprint groups. Both groups identified that RWE creates an iterative, high-priority opportunity to inform conditional reimbursement recommendations/decisions, understand product place and performance in routine clinical practice in terms of comparative safety, effectiveness, and cost-effectiveness, and expand or contract appropriate use in terms of patient profiles, indications, and place in care pathways. RWE was also consistently identified as a high-priority mechanism to assess the economic value of a therapy and adjust pricing and reimbursement recommendations and decisions as appropriate.

In terms of priorities for phase-in opportunities, both groups noted that choices made were in the context of the case study provided, and that evaluation of priority could change for different circumstances. Both groups saw a clear phase-in opportunity for RWE to inform/enable conditional reimbursement with a coverage with evidence development approach. This decision was driven by the perceived value for RWE to support this type of decision-making, and the potential for this use case to be of lower risk than one to inform a regulatory decision.

In the deliberate absence of definitions provided to characterize *quality*, it was generally defined by both groups as the degree of rigour required, or the threshold of evidence needed in order to make a decision. In the discussions, quality was viewed and considered from the perspective of the stakeholder making a decision, and the ramification(s) of the decision. The sprinters generally, and appropriately, interpreted the quality assessment as a relative exercise, and stated that lower quality

requirements were not intended to express support for low-quality evidence, but rather to suggest opportunity for an increased ability to adapt interpretation to the context (including other evidence that is available).

In terms of the assessment of the relative quality required for RWE to be *decision-grade*, the bias of the sprinters was towards the highest quality being required when used to support regulatory decisions. There appeared to be greater comfort with a lower degree of required quality when RWE is used to support HTA/reimbursement decision-making, and where there is greater opportunity for RWE to serve as one input amongst others that are included in the total body of evidence informing a decision.

A conclusion from the quality discussion is that, in terms of developing a quality framework, we should articulate an ideal future state reflective of the highest quality possible, but also consider how a framework can be practically implemented in the near term to support RWE generation and utilization for important decisions where there is uncertainty. In other words, a developed framework should have enough rigour and precision to be helpful, but also enough flexibility that it is realistic, implementable, and can be accepted and used in a case-dependent, context-specific manner in light of the opportunities and limitations that we currently have.

3.3. RWE Quality Standards

For the next section of the design sprint, sprinters worked within a one-hour timeframe to articulate the quality standards required, and methods to assess RWE against standards, for a priority use case. Sprinters across the two groups were challenged to define specific standards for RWE quality. Quite reasonably, the sprinters consistently identified that the value and use of RWE will be highly context-dependent, and, as such, there is a need to consider each opportunity for RWE on a case-by-case basis. That said, a number of themes emerged from both sprint group discussions that are instructive to support the increased phasing-in of RWE along the decision continuum going forward. The following key themes were uncovered during the discussions.

The process followed is as important as any defined standards

Given that RWE generation and utilization is very context-specific, it is challenging to articulate prescriptive guidance that is intended to be closely followed. Rather, it is advisable to articulate a good process to follow, that leads to the highest quality RWE that will be of the greatest value to decision-makers.

Look to good research practices currently in use for guidance on RWE

There may not be a need to identify specific, unique approaches for RWE in guidance that is produced, rather well-accepted practices (for example, representativeness of patient populations studied, appropriate sample sizes) from existing fields such as epidemiology and statistics can serve to shape an acceptable approach to RWE.

Develop a framework to identify the context, and to guide key aspects of RWE generation

A framework incorporating well-defined acceptable practices from relevant fields that defines a structured decision-making process for RWE generation will be useful to identify conditions of acceptability of RWE to decision-makers. We should learn and align with other jurisdictions completing similar work, for example the Duke-Margolis RWE Collaborative in the United States which structures RWE considerations around the regulatory and clinical context for the decision

problem, and offers considerations for data (for example, completeness, reliability, validity) and methods (study design and credibility), which collectively leads to fit-for-purpose RWE.

Involve key stakeholders and gain agreement at the outset

Given the need for judgement and good planning, and in the absence of implementable guidance articulating clear standards intended to be closely followed, stakeholder engagement and participation is critical. An inclusive and collaborative approach will permit those who sponsor, generate, and use RWE to have a voice when following a structured RWE development process, reducing uncertainty, ensuring clarity on the decision problem to be informed, and increasing the expected value of the RWE. How and what decisions will be made on the basis of the RWE generated should be clear and agreed to at the outset (for example, a priori establishment of metrics to be considered, thresholds, how they may be considered in context of other evidence, and what decisions they will drive).

Trust is key

Trust between stakeholders is critical for successful collaboration. Trust depends on the distribution of risk, and less risk for each stakeholder can result in increased trust. Risk is proportional to uncertainty; with less uncertainty comes less risk and more trust. A clear, inclusive, structured process to develop and use RWE will decrease uncertainty, reduce risk, and create trust.

We can learn by doing

As we gain experience with RWE to support specific decision problems, over time we will learn and be in a better position to recommend a more consistent and standard approach to achieving quality. This will support scale of RWE and less resource-intensive approaches to RWE generation and utilization.

Start with something simple

There is opportunity currently to start with some of the priority use cases identified at this workshop and phase-in the use of RWE to support decision-making. We can start with something that is relatively more simple, of lower risk in terms of decision consequence, learn, achieve some early wins, and gain some trust. To do this we need to be equally comfortable with being uncomfortable, and be comfortable with the discomfort.

3.4. RWE Implementation Considerations

The last section of the design sprint brought both groups together for a one-hour discussion of life cycle evidence development plan implementation considerations. The following questions were posed to the participants.

1. What guidance is required?
 - From Health Canada and CADTH to guide collection of RWD and the generation and submission of RWE to implement the plan?
2. How do we ensure generation of and access to necessary, high-quality data?
 - What should be done to optimize the collection, use, and quality of data sources (both existing and new) to meet our collective RWD needs?
3. What are the main challenges to be anticipated with increased use of RWE?

Similar to the previous discussion on the quality required for a priority use case for RWE, the group indicated that detailed, prescriptive guidance is not practical or feasible. Rather, guidance will need to be at a principle or factors/considerations level in order to be implementable, should ideally be aligned with emerging international standards to inform a Canadian approach, and should be considered in terms of a planned series of updates over time as we learn by doing. It was recommended that the development of guidance occur through a very collaborative approach, with all stakeholders participating. It was noted that guidance should not just be considered for the biopharmaceutical industry, but also for the research community, data custodians, and those who provide the technical and infrastructure support to process and analyze data. In addition to considerations for RWE data sources and study design, it was suggested that prioritization and sharing of which areas of focus or policy questions are considered to be most important by Health Canada, HTA agencies, and payers would be helpful to focus the initial efforts of industry and the research community.

Moving forward, a standing, sustainable forum for multi-stakeholder dialogue, similar to initiatives in Europe and the United States, was encouraged. The group reinforced that we currently have the data and technical capabilities/methods to produce quality RWE, and the biggest challenge is aligning stakeholders and building trust. It was recommended that we learn from previous experience, such as with conditional reimbursement and risk-sharing agreements, and understand how to overcome barriers that have been encountered (for example, data ownership, distribution of risk, legal/ethical considerations) in order to accelerate the phasing-in of a greater role for RWE to inform decision-making.

4. Concluding Comments

The design sprint workshop represented a good start in terms of a broad group of stakeholders coming together to discuss, in a concrete manner, complex and challenging issues related to an increased role for RWE to inform decision-making across the product life cycle. A rich and productive discussion took place, with stakeholders from different perspectives engaging and sharing experiences and considerations. Clearly this workshop was a good start; however, there is much more to do to articulate, implement, and monitor a thoughtful and sustainable Canadian approach and guidance for phasing-in a more meaningful role for RWE. The level of interest and engagement at this workshop suggests that the stakeholder community is prepared and willing to continuously be engaged to move the conversation forward, and to participate in similar future forums and working groups to support Canada to better utilize RWE to inform important decision-making across the pharmaceutical product life cycle, with the objective to improve appropriate access to necessary therapies for Canadians.

Appendix A: Workshop Program

CAPT Conference Workshop

October 21, 2018

**Chelsea Hotel, Rossetti Room
33 Gerrard St W, Toronto**

Workshop Title

Defining “Decision-Grade” Real World Evidence (RWE) and its Role in the Canadian Context: A Design Sprint

Objectives

1. To identify the value and applications of RWE in supporting pharmaceutical regulatory and reimbursement decision-making.
2. To identify the conditions upon which RWE will be considered of sufficient quality to inform decision-making.

Agenda

Time	Topic	Presenter/Facilitator
9:00-9:15	Welcome & Design Sprint Overview	Allan Gillman
9:15-10:15	Lightning Talks	Tammy Clifford, Rhonda Kropp, Kelvin Chan, Michael Duong
10:15-10:30	Break	
10:30-10:45	Design Challenge Statement & Case Study Presentation	Dan Palfrey
10:45-12:45	Identification of Applications of RWE (Breakout Rooms – Sprint 1)	Kimberly Robinson, Peter Dryda
12:45-1:30	Lunch	
1:30-2:30	Identification of “Decision-Grade” Quality Standards (Breakout Rooms – Sprint 2)	Kimberly Robinson, Peter Dryda
2:30-2:45	Break	
2:45-3:45	Identification of Implementation Considerations	Dan Palfrey
3:45-4:00	Wrap-Up & Adjourn	Tammy Clifford, Rhonda Kropp

Speaker Biographies

Rhonda Kropp

Rhonda Kropp is currently the Director General for the Marketed Health Products Directorate in the Health Products and Food Branch of Health Canada. She is responsible for the oversight of the vigilance of marketed health products in Canada, including ensuring Canadians and health professionals are informed of important issues impacting the safety and effectiveness of health products in a timely fashion.

Rhonda has been working in health policy, programs and surveillance for over 20 years as a nurse, microbiologist, researcher and infectious disease epidemiologist. She undertook her graduate training in public health at the University of California, Berkeley. After a few years directing public health research projects in California for the state government, Stanford University and the University of California, San Francisco, Rhonda joined the Government of Canada in 2003.

During her fifteen years with the Government of Canada, Rhonda has taken on a diversity of roles in the federal health portfolio in the areas of sexual health, travel health and infectious disease prevention and control before joining the regulatory environment. Rhonda was the proud recipient of the Chief Public Health Officer of Canada medal in 2017.

Dr. Tammy Clifford

Dr. Tammy Clifford is presently CADTH's Chief Scientist and Vice President, Evidence Standards. Over the past dozen years, she has held a number of senior leadership roles at CADTH. She is actively engaged in many national and international HTA activities, including serving as a deputy editor with the *International Journal of Technology Assessment in Health Care*, and was the co-chair of the International Scientific Programme Committee for HTAi 2018, that was held in Vancouver in June 2018. Tammy holds a PhD in Epidemiology & Biostatistics, and is on faculty with the University of Ottawa's School of Epidemiology and Public Health. At the end of October, Tammy will become the Vice President, Research Programs at CIHR.

Dr. Kelvin Chan

Dr. Kelvin Chan is a medical oncologist at the Sunnybrook Odette Cancer Centre, an associate professor at the University of Toronto, and an associate scientist at the Sunnybrook Research Institute. He specializes in GI oncology and head and neck oncology. As a clinical epidemiologist and biostatistician, Dr. Chan's research interests include health services research, health technology assessment, meta-analysis including network meta-analysis, cost-effectiveness analyses, and statistical methods research in health economics. He is co-director at the Canadian Centre for Applied Research in Cancer Control, funded by the Canadian Cancer Society. Professionally, Dr. Chan has an interest in cancer drug reimbursement related issues. He is a member of multiple provincial and national committees related to cancer drug assessments and recommendations including the Committee to Evaluate Drug, and the Ontario Steering Committee of Cancer Drugs, which he currently chairs. He is also the clinical lead for the Provincial Drug Reimbursement Programs at Cancer Care Ontario.

Dr. Michael Duong

Dr. Michael Duong is the Director for Personalized Healthcare and Evidence Generation in Medical Affairs for Hoffmann-La Roche Limited. In this role, Michael manages a team responsible for medical research in Canada, including clinical trials, real world data sciences, health outcomes research, and biostatistics. In addition, Michael is responsible for Roche's strategy to advance the personalization of healthcare in Canada. Prior to that, Michael led Health Economics at Roche in the Reimbursement and Health Economics Department. In that role, Michael provided expertise and guidance over the health economic and outcomes research activities conducted at Roche Canada. Prior to that Michael spent three years in health care consulting, specializing in health economics and outcomes research, and medical communications. Michael received his undergraduate degree in Biology and Pharmacology and a Ph.D. in Medical Sciences with a specialization in Neuroscience, both from McMaster University.

Appendix B: Workshop Registrant Affiliations

Sprinters	
Alberta Health Services	Health Canada
Alberta Ministry of Health	Institut national d'excellence en santé et en services sociaux (INESSS)
Amgen	Institute for Clinical Evaluative Sciences
Astellas	IQVIA
Bayer	Janssen
BC Cancer Agency	Kidney Cancer Canada
CADTH	Medlitor
Canadian Association for Population Therapeutics	Merck
Canadian Breast Cancer Network	Novartis
Canadian Cancer Survivor Network	Ontario Drug Benefit Program
Canadian Institutes for Health Research	Ontario Ministry of Health and Long-Term Care
Canadian Network for Observational Drug Effect Studies (CNODES)	Ontario Drug Policy Research Network
Canadian Pharmacists Association	pan-Canadian Pharmaceutical Alliance
Cancer Care Ontario	Roche
CancerCare Manitoba	Sanofi
Celgene	Saskatchewan Ministry of Health
Colorectal Cancer Canada	St. Michaels Hospital
Dalhousie University	University of Toronto
GlaxoSmithKline	
Observers	
Allergan	Innomar Strategies
Amaris	Innovative Medicines Canada
Amgen	J. L. Glennie Consulting
Astellas	Janssen
AstraZeneca	Leo
Bayer	McGill University
BIOTEC Canada	McMaster University
Boehringer Ingelheim	Memorial University
Bristol-Myers Squibb	Merck
Case Market Access Consulting Inc.	Novartis
Eisai	Novo Nordisk
GlaxoSmithKline	Ontario Public Drug Programs
Hoffmann-La Roche Ltd.	Takeda
Hope Research Center	University Health Network

Appendix C: Design Sprint Case Studies

Case Study 1

Disease Y is a rare cancer that primarily affects the nervous system. In the late infantile form of the disease, signs and symptoms typically begin between ages 2 and 4. The initial symptoms typically include language delay, recurrent seizures and difficulty coordinating movements. Affected children also develop muscle twitches and vision loss. Disease Y affects essential motor skills, such as sitting and walking. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past adolescence. Drug B is already on the market to treat Disease Y; however, a new treatment, Drug X, has been submitted for authorization to Health Canada and is the first treatment developed with the aim to slow loss of walking ability in symptomatic paediatric patients with Disease Y.

The efficacy of Drug X is to be evaluated in a non-randomized, single-arm dose escalation study in symptomatic paediatric patients with Disease Y and will be compared to untreated patients with Disease Y from a natural history cohort (an independent historical control group) who are at least 3 years old and have motor or language symptoms. Walking ability is to be the primary outcome of interest.

The manufacturer conducted the proposed efficacy study and recruited 22 symptomatic paediatric patients with Disease Y and identified 42 untreated patients with Disease Y from a natural history cohort. Taking into account age and baseline walking ability, Drug X-treated patients demonstrated fewer declines in walking ability compared to untreated patients in the natural history cohort.

The safety of Drug X was evaluated in 24 patients with Disease Y aged 3 to 8 years who received at least one dose of Drug X in the clinical study. The most common adverse reactions in patients treated with Drug X were fever, ECG abnormalities, slow heart rate, hypersensitivity to tactile stimulation, change in CSF protein level, vomiting, seizures, abnormal collection of blood outside of a blood vessel, headache, irritability, increased CSF white blood cell count, feeling jittery and low blood pressure.

Comparative effectiveness with Drug B has not yet been assessed.

Key Questions to Consider

1. What are the key problems with the current evidence base for Drug X (which represents a treatment for a rare condition) in terms of safety, efficacy and effectiveness?
2. What are the potential roles and value of RWE throughout the life cycle of Drug X?
3. Would the quality of data required along the life cycle differ depending on the specific questions at hand? If so, how?
4. If NOC/c market authorization was granted for Drug X, how can the promising evidence be confirmed?

Other Questions for Consideration

1. What measures should be put in place (if any) to continue to monitor the safety and effectiveness of Drug X?
2. How can long term data be captured regarding this drug prescription and effects? What data elements should be captured for monitoring safety, efficacy, or effectiveness?

3. Are there other risks of off-label use, beyond treatment of Disease Y? How can off-label use be monitored?
4. What comparative effectiveness trials would you recommend to establish the safety and efficacy of Drug X to Drug B?
5. Should RWE be acceptable for inclusion in submissions for HTA and Regulatory purposes? If so, how can promising evidence be assessed?

Case Study 2

Drug Z is indicated for use as an adjuvant treatment for prostate cancer in addition to Androgen Deprivation Therapy (ADT). This new drug has a unique mechanism of action that does not cause the same side effects as ADT. Typical side effects with ADT include hot flashes, loss of energy, decreased libido, and weight gain. ADT is also associated with long-term impacts on bone quality which increase the risk of fracture. The efficacy of Drug Z was evaluated in randomized double-blind clinical trials as an add-on therapy to ADT for the treatment of prostate cancer, and has been approved by Health Canada for this indication. Drug Z is being submitted for review by HTA agencies.

There is a trend observed towards reduced fracture risk with Drug Z in combination therapy with ADT. However, the evidence from the clinical trial program to suggest reduced fracture risk with Drug Z is inconclusive, and not sufficient for an expanded indication related to fracture risk reduction in combination therapy with ADT. Additionally, estimates on reductions in serious fractures are not currently available. This greatly impacts inputs into economic evaluations, which in turn will impact the suggested pricing of the drug. Importantly, current trials are ongoing for the potential use of Drug Z as monotherapy in patients with increased risk of fracture and those intolerant to ADT. The results of these trials are not expected for another 2 years.

Key Questions to Consider:

1. What are the key problems with the current evidence base for Drug Z (which represents a treatment for a more prevalent condition), in terms of safety, efficacy and effectiveness?
2. What are the potential roles and value of RWE throughout the life cycle of Drug Z?
3. Would the quality of data required along the life cycle differ depending on the specific questions at hand? If so, how?

Other Questions for Consideration

1. What data elements should be captured for monitoring safety, efficacy, or effectiveness?
2. What measures should be put in place (if any) to continue to monitor the safety and effectiveness of Drug Z?
3. Should RWE be acceptable for inclusion in submissions for HTA and Regulatory purposes? If so, how can promising evidence be assessed?
4. What studies would you recommend to establish the safety and efficacy or effectiveness of Drug Z?

This report provides a summary of a real-world evidence (RWE) design sprint workshop that took place on October 21, 2018 in Toronto, Ontario. The workshop was developed and delivered as a joint partnership between the Canadian Agency for Drugs and Technologies in Health (CADTH); Canadian Association for Population Therapeutics (CAPT), Health Canada, and the Institute of Health Economics (IHE). The intent of the workshop was to identify key opportunities for RWE to support decision-making throughout the pharmaceutical product life cycle, as well as the evidence standards required to be considered decision-grade.



Health
Canada

Santé
Canada



Report published by the Institute of Health Economics
1200 – 10405 Jasper Avenue
Edmonton AB Canada T5J 3N4
Tel. 780.448.4881 | Fax. 780.448.0018
info@ihe.ca | www.ihe.ca

ISBN 978-1-926929-93-4 (online)