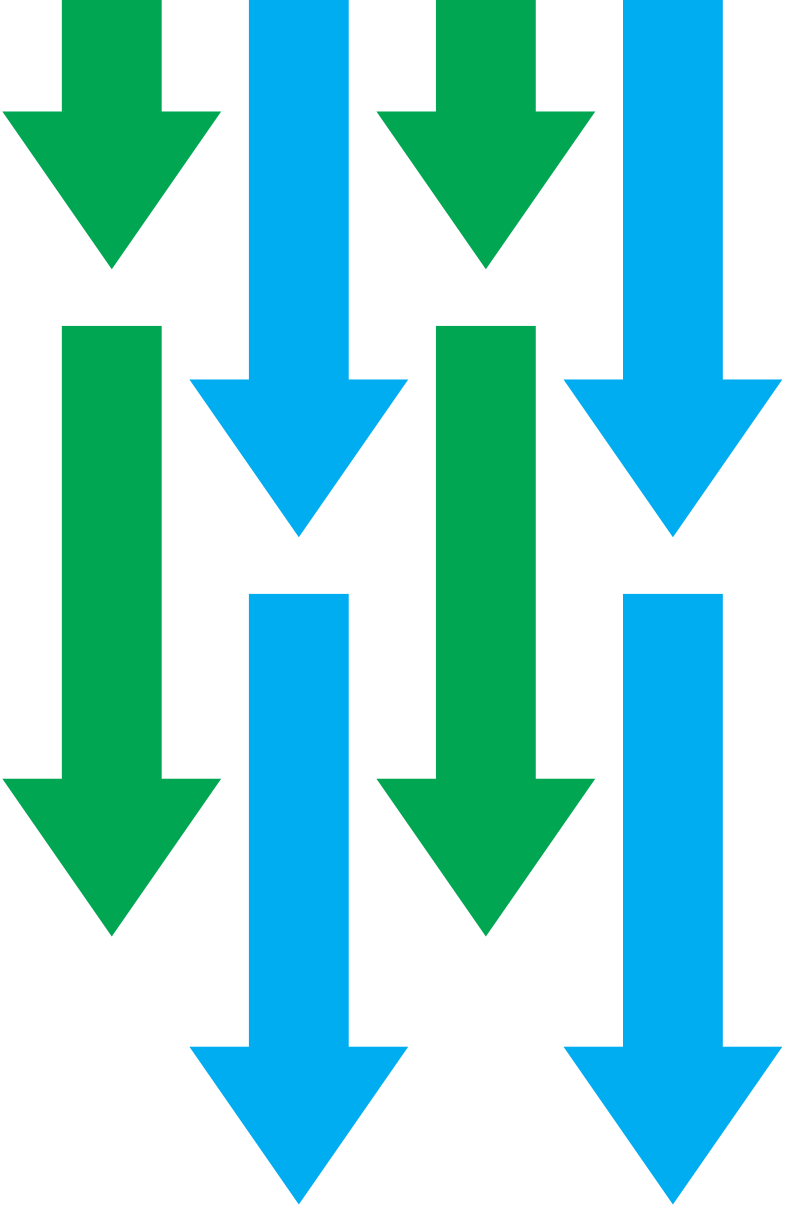


Report on a Best Brains Exchange

Optimizing the Use of Real-World Evidence as Part of Decision-Making for Drugs for Rare Diseases

Chairs

Canada's Drug and Health Technology Agency

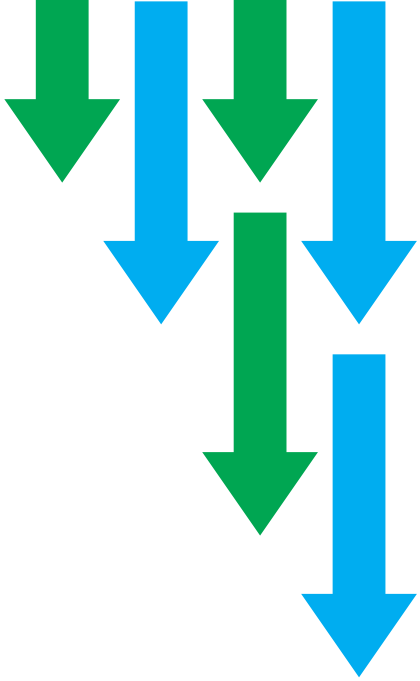
CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

CORD Canadian Organization for Rare Disorders

Observers

Health Canada

July 2022



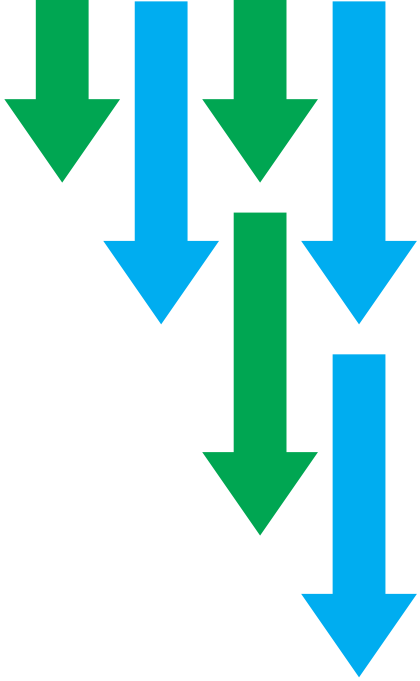
Abbreviations

BBE	Best Brains Exchange
CIHR	Canadian Institutes of Health Research
CORD	Canadian Organization for Rare Disorders
HC	Health Canada
HTA	health technology assessment
NLP	natural language processing
RWD	real-world data
RWE	real-world evidence

Terminology

Real-world data An umbrella term for data collected outside of the randomized clinical trial paradigm including data from medico-administrative databases, registries, observations from clinical practice, and patient-reported information

Real-world evidence Evidence derived from the analysis of data collected outside of randomized controlled trials that is considered complimentary, not a replacement.



Executive Summary

The objective of this Best Brains Exchange (BBE) was to share perspectives and discuss how to optimize the use of real-world evidence (RWE) as part of decision-making for drugs for rare diseases.

Over 2 days in the fall of 2021, 137 participants from Canadian stakeholder groups that collect, hold, analyze, and use data for regulatory and health technology assessment (HTA) purposes exchanged ideas and discussed a fictious rare disease treatment model.

The discussions identified 2 overarching themes for consideration relating to the use of real-world data (RWD) and RWE for decision-making pertaining to rare diseases in Canada: collaboration and data.

An enhanced ecosystem of collaboration between members of the regulatory, health technology, and payors landscape emerged as an important consideration for participants. Multi-stakeholder dialogue was considered an important tool to implement in the assessment of rare diseases and associated decision-making procedures related to rare diseases. Important parameters included:

- identifying key stakeholders and their respective roles (e.g., patients, industry, payers, researchers, clinicians, regulators)
- determining how stakeholders will work together
- establishing an infrastructure for collaboration, including funding considerations.

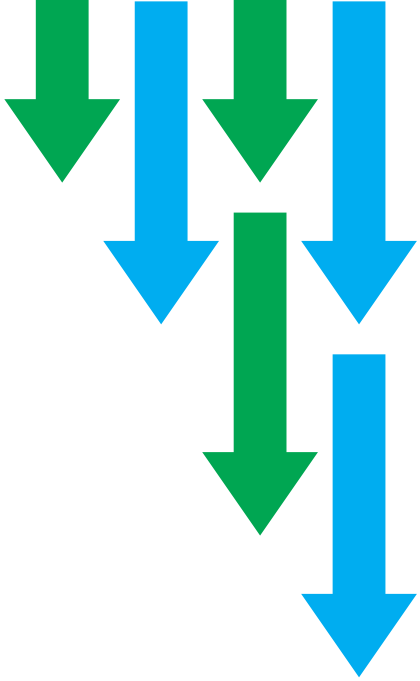
The importance of enhanced access to quality data in the form of RWD was the second most commonly discussed theme at the BBE. Participants discussed key issues such as:

- collecting high-quality RWD to resolve uncertainties (e.g., natural disease history)
- identifying the best sources of RWD for decision-making
- increasing confidence in the current methods and use of RWD
- generating RWD to bridge gaps in clinical trial evidence and contextualize results to the real-world Canadian health care setting.

Participants identified multi-stakeholder dialogue, clear and transparent governance of RWD generation and its use by a neutral organization, and enhancements in the health system infrastructure as important requirements for successful collaboration and engagement and for optimizing the use of RWE for decision-making about drugs for rare disease in Canada.

Next Steps

Following the BBE, Health Canada, the Canadian Institutes of Health Research (CIHR), CADTH, and the Canadian Organization for Rare Disorders (CORD) have initiated action to optimize the use of RWE for decision-making about drugs for rare diseases. These groups will collaborate on learning projects through the establishment of an RWE Steering Committee chaired by CADTH and Health Canada. A summary of each of the quarterly meetings of the RWE Steering Committee will be posted on CADTH's new RWE website.



Introduction

Background

There are 6,000 to 7,000 rare diseases,[1] of which only 7% have an approved treatment. Of all rare diseases, 72% have a genetic origin.[2] The combination of genetic information and patient-relevant outcomes drives research and development of the next generation of targeted therapies to reduce symptoms and disease progression and potentially enables prevention and cure. Innovative therapies are increasingly based on small and short-term clinical trials; therefore, additional evidence from the real-world setting — particularly about longer-term outcomes — may be needed to support the evidence base required for regulatory approval and HTA. Measurement of these outcomes will be a key component to a life-cycle approach for decision-making and may be part of innovative access schemes such as managed access plans or outcomes-based agreements.

Policy Context

Efforts are underway to help people with rare diseases living in Canada access safe and effective care. Collaborative learning is key to building a Canadian framework for more streamlined and better-informed decision-making that will optimize access to treatment for rare diseases. Collaborative learning will also play an integral role in informing the development of a national strategy. It is important to understand the information needs and the availability and quality of evidence from the real-world setting to support regulatory and HTA decision-making. Current methods, data collection infrastructures, and resources involving a range of stakeholders will need to be enhanced to develop RWE that is sufficiently robust to inform decision-making about drug approval, reimbursement, and optimal use.

BBE Event

In October 2021, the Canadian Institutes of Health Research (CIHR), CADTH, the Canadian Organization for Rare Disorders (CORD), and Health Canada collaborated to hold a 2-day BBE to promote and coordinate discussion about the optimal integration of RWE for decision-making about drugs for rare diseases. The event was chaired by Christopher McMaster, Scientific Director, Institute of Genetics, CIHR.

The BBE brought together 137 invited participants from across Canada with a cross-section of different types of health system stakeholders (Figure 1):

- Health Canada representatives
- HTA scientific professionals (CADTH and INESSS)
- CIHR
- CORD/patient perspective representatives
- care providers
- academics/methodologists
- industry representatives
- public payers, pan-Canadian Pharmaceutical Alliance (pCPA) members
- policy-makers
- private payers
- rare disease registry data holders
- medico-administrative database representatives.

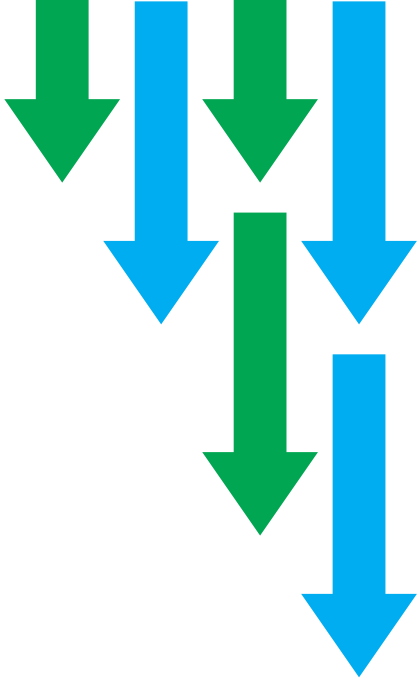


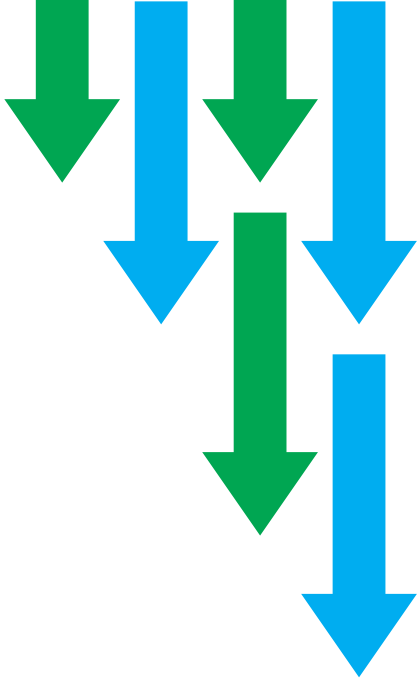
Figure 1: Distribution of BBE Participants by Stakeholder Group

- Academic Care Providers (**4%**)
- Academics/Methodologists (**6%**)
- CIHR (**6%**)
- Health Canada (**18%**)
- HTA Bodies (CADTH and INESSS) (**14%**)
- Industry (**9%**)
- Medico-administrative Data Holders (**6%**)
- Patient Experts and Organizations (**8%**)
- Patient Perspectives (**2%**)
- pCPA and Public Payers (**9%**)
- Policy Makers (**7%**)
- Private Payers (**6%**)
- Registry and Data Holders (**6%**)

Objectives

The overarching goal of the BBE was to share perspectives and discuss how to optimize the use of RWE as part of decision-making for drugs for rare diseases. The specific objectives included:

- understanding different stakeholders' perspectives on the role of RWE in decision-making about drugs for rare diseases at different points in the drug life cycle
- evaluating the potential value of RWE to fill gaps in evidence about the treatment of a rare disease at different points in the drug life cycle
- understanding the potential value of RWE to fill evidence gaps about the treatment of a rare disease and streamline the decision-making process toward patient access (with conditions that include data collection)
- identifying the challenges and keys to multi-stakeholder collaboration that successfully streamline processes while providing the necessary information for decision-making at different points in the drug life cycle
- identifying next steps toward strengthening RWE for decision-making about drugs for rare diseases in Canada.



Methods

The BBE ran virtually over 2 half-days in October 2021. The program agenda and structure (Appendix 1) were developed collaboratively by representatives of the co-host organizations and a representative of the RWE4Decisions international initiative. The event included an introduction to the day, the presentation of a fictitious case, a plenary session, expert panel sessions, and breakout group discussions.

Two background papers about the use of RWE for decision-making in other countries were sent to participants in advance of the event.[3,4] To guide discussion, a fictitious case study was presented for a new 1-time gene therapy for treatment of a rare pediatric disease. The clinical data presented included information about patient age, genotyping, clinical trial parameters, adverse safety events, and clinically desired outcomes (Appendix 2). The fictitious decision context indicated that the drug had been conditionally reimbursed in other countries with specific RWD collection requirements.

Questions about the context of the fictitious case were clarified in a plenary session. Representatives from different stakeholder groups gave their initial reflections about the gaps in the presented clinical evidence (uncertainties) from their decision-making perspective. Discussion about the evidence gaps and uncertainties was then opened to all participants in a plenary session. Participants were then assigned to smaller group discussions. The goal of the small group discussions was to give participants an opportunity to experience and test a new form of a multi-stakeholder advice meeting. Participants were asked to share their perspectives about whether RWD collection might be feasible in Canada to enable a re-appraisal of evidence in 5 years with the assumption that the initial appraisal of the fictitious case was positive but raised some important uncertainties.

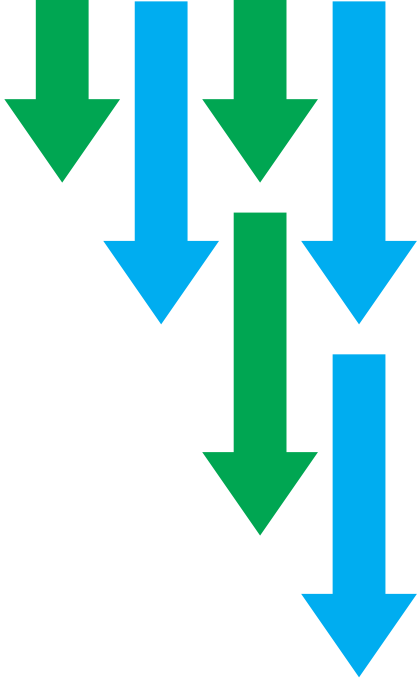
There were 5 multi-stakeholder groups with diverse stakeholder representation. Each group also had a designated moderator and scribe. Key insights from the breakout groups were shared with all participants in feedback sessions.

The breakout groups addressed the following questions on the **first day:**

- What RWD should be collected to develop evidence that can resolve the uncertainties for future decisions about whether treatment should continue to be made available and how its use should be optimized (e.g., population to be treated)?
- Where can we get those RWD — from Canada or internationally — and what sources would we trust?
- What would increase our confidence in the results of RWE (methodological rigour, independence, meaningful patient involvement, confidence in the team doing the analysis)?

The breakout groups addressed the following questions on the **second day:**

- What kind of collaboration do we need among stakeholders?
- What is needed to support collaboration (infrastructure?) to collect RWD (e.g., contracts, processes)?
- How do we leverage international collaboration from jurisdictions where there may be earlier access to treatment, published data collection plans, and RWE?
- Who owns the data and who can do what with the data, intellectual property, and so on?
- Who is going to collect the data and pay for it?
- Who has responsibility for what and how will there be oversight as the data collection progresses?
- How can we ensure the RWE generated will be used in future decision-making by HTA/payers (and what is the value of the RWD)?



The meeting ended with an overall exchange of ideas about how RWE could be integrated into decision-making in Canada.

Participants were encouraged to have open dialogue with the assurance of confidentiality in accordance with the Chatham House Rule which has a guiding spirit of sharing information without revealing the identity of who shared it. The event was recorded, and a transcript was generated to facilitate analysis of the discussion.

Analysis

CADTH coordinated a rigorous analysis of the discussion transcripts of all 5 breakout groups from the 2 days, which included the use of natural language processing (NLP) software (NVivo) in collaboration with an NLP expert. Notes from the BBE transcript that summarized the information by key messages and by stakeholder group were used for the NLP analysis. The expert NLP analyst and the CADTH team used an inductive approach to content analysis (i.e., codes are defined from the data and refined during the data analysis process). A more detailed description of the methods used in the NLP analysis is available in Appendix 3.

Results of the NLP analysis included points of consensus, key representative quotes, additional perspectives without consensus, data visualization, and barriers and facilitators to integration of RWE in decision-making through multi-stakeholder collaboration.

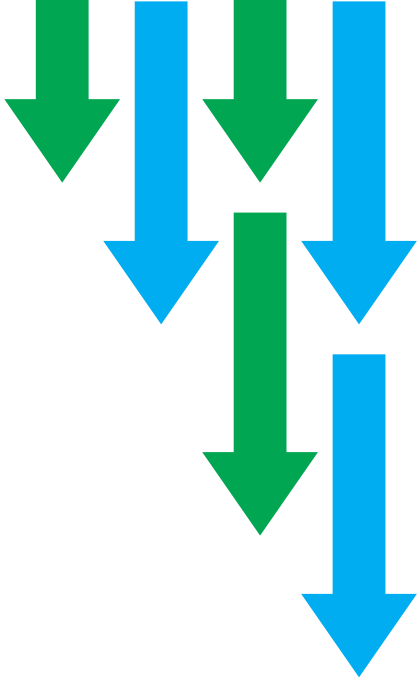
A full overview of the multi-stakeholder dialogue can be found in Appendix 4, Appendix 5, and Appendix 6.

Results

Key Themes

Two main themes of discussion were identified from the NLP analysis: collaboration and RWD. The collaboration theme includes factors that the participants identified as important to successful collaboration and engagement, such as multi-stakeholder dialogue, governance, and infrastructure. The RWD theme included participant discussion about all aspects of gathering and using RWD as RWE for decision-making, such as identifying gaps in evidence, what RWD to collect, where to collect RWD (sources of data), limitations of RWD, and how to increase confidence in RWD among stakeholders. The perceived importance of the BBE in facilitating change is reflected in the following quote:

- "This is a watershed moment."



Collaboration

The most highlighted issue during the BBE was linking stakeholders for a common purpose around RWE generation and analysis to support decision-making:

> "There is an opportunity here for multiple stakeholders to work together to generate high-quality evidence to suit multiple needs, including those of the regulator, industry, HTA, payers, clinicians, etc."

Participants felt collaboration should ideally be at the national level to support the use of larger datasets but that jurisdictional differences may affect this goal. These differences include legislative differences related to informed consent, regulations around data collection and storage, consistency in data reporting, and the availability of suitable national datasets.

It was noted there is already some infrastructure in place that can be leveraged for learning as well as collaborations with Canadian and international groups that have already been successful with this kind of work.

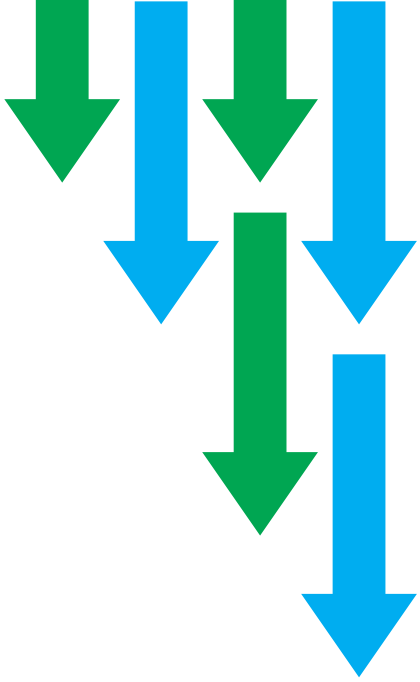
An additional early step for building collaboration is the development of a clearly defined governance structure. Key elements for successful governance include representation from multi-stakeholder groups and a clear outline of roles. Further, processes related to RWD collection, storage, ownership, intended use, and access permissions should be defined as part of governance. Preparation of protocols, assurance of data quality, and data analysis accountability also need to be addressed. These steps will assist in ensuring that RWD is high quality, meets the evidence needs of users, and supports quality decision-making. Finally, the value of investing in RWE can be demonstrated only with a strong governance structure in place as described. Although there is a willingness to collaborate, it is important to define the roles of stakeholders and involve all stakeholders at the outset as much as possible. It was mentioned that further consideration should be given to the inclusion and role of patient caregivers to garner their perspective. Also identified was a need for transparency in discussions and building trust among stakeholders.

A more in-depth analysis of the discussion on the basis of NLP, including a list of topics discussed for the collaboration theme, are presented in Appendix 6.

Real-World Data

The discussion centred on parameters such as identifying the types of data necessary to resolve current uncertainties in the use of RWD for decision-making and the data sources that are currently available or will need to be in the future. A suggested path forward involves planning RWD generation through early and iterative multi-stakeholder dialogues including:

- consideration for patient and caregiver perspectives
- enhanced data collection of population subgroups (e.g., Indigenous people and patients)
- collecting qualitative and quantitative data
- collecting data related to disease-based outcomes versus drug-specific outcomes (e.g., quality of life, economic outcomes)
- applying a standardized approach to data collection
- placing an increased emphasis on natural histories and disease progression.



As stated by a participant:

> "Have the patients as key stakeholders, bringing the patients voice can help identify the best outcomes to track."

It was evident that there is a demand for enhanced governance and guidelines for the collection and application of RWD to support decision-making, including how these data are collected, processed, analyzed, and mobilized within Canada or in collaboration with other countries or jurisdictions. Broad agreement on standards about generation and use of RWD will be required among stakeholders.

RWD sources, data access, quality, and consistency may vary by jurisdiction and by stakeholder group. Data elements deemed suitable for measurement or for supporting decision-making may also be highly variable, with considerations about feasibility and reliability, and the availability of measurement tools being key. Capture of information about quality of life was raised as an example of an important outcome that is associated with challenges in terms of feasibility and reliability.

In rare diseases, data capture is further challenged by small sample size. There is interest in, need for, and benefit to collaborating across jurisdictions to increase dataset size to facilitate more meaningful analysis. In response to the infrastructure and dataset requirements with small populations, there was debate about 2 models: 1 registry for all rare diseases that collectively captures a common dataset across diseases with additional data capture that is specific to each disease and multiple disease-specific registries that can be combined as required through a common platform. Combining Canadian and international RWD or comparing Canadian RWD with international RWD could be explored but comes with the additional consideration of contextual differences. It would be important to ensure these data represent the health care systems and a quality of life comparable to the Canadian health care setting. The following statement highlights many of the ideas expressed in relation to the theme of RWD:

> "It is critical that, a multi-stakeholder team comes together right at the inception of the design to say what kind of data is needed and what are going to be the caveats around the quality of that data."

A more in-depth analysis of the discussion on the basis of NLP, including a list of topics discussed for the RWD theme, can be found in Appendix 7.

Visualization of Results of BBE Discussions

Data visualizations such as word clouds can illustrate the themes raised at the BBE. The 3 word clouds created present the most frequently used words (red, bold, larger font) on day 1 (Figure 2), day 2 (Figure 3), and during the entirety of the exchange (Figure 4). Other words in the cloud that are bolded and in larger font were used more frequently than unbolded words with smaller font.

Figure 2: Word Cloud for Discussions From BBE Day 1

Note: Words that are blue, bold, and in larger font represent the most frequently used words.

Figure 3: Word Cloud for Discussions From BBE Day 2

Note: Words that are blue, bold, and in larger font represent the most frequently used words.

Figure 4: Combined Word Cloud for Discussions From BBE Days 1 and 2

Note: Words that are blue, bold, and in larger font represent the most frequently used words.

Barriers and Facilitators

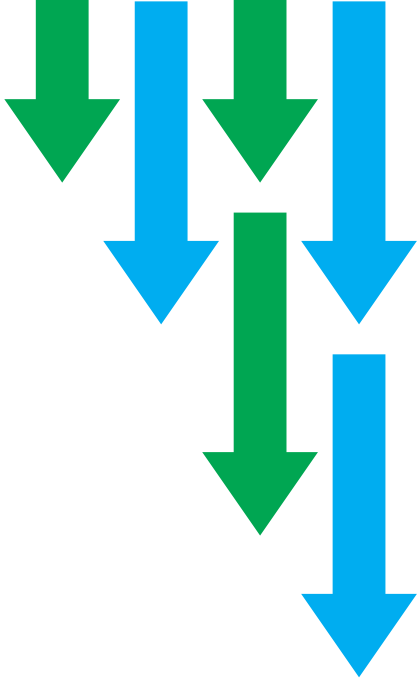
This section summarizes the most frequently stated barriers and facilitators to multi-stakeholder collaboration in the domain of RWD and RWE for decision-making about drugs for rare disease.

Barriers

Barriers to collaboration include challenges associated with working across jurisdictions when there are differences in legislation, regulation, and informed consent. Information needs are also highly variable across stakeholder groups and across types of rare disease. Although some infrastructure is in place, this infrastructure should be enhanced with attention paid to linking data between different databases, alignment, and consistency of RWD elements, appropriate data collection methods, and the availability of resources for RWD generation when required. Trusting relationships must be developed among stakeholders, especially with patients and caregivers, so that effective collaboration can be realized.

Facilitators

There is goodwill among stakeholder groups and an acknowledgement of the advantages of collaboration. However, establishment of a multi-stakeholder group to develop a strong governance structure with clear and transparent terms of reference can support this goodwill and facilitate trusting relationships. It will be essential to partner with a neutral organization with expertise in facilitating collaboration, leveraging RWD, and administering the established processes and protocols included in the governance structure. Within the governance structure, guidelines must be developed



collaboratively a priori that focus on fitness for purpose and associated processes for gathering, analyzing, using, and reporting RWD. Canadian and international collaboration models could serve as examples for rare disease RWE initiatives.

Participant Evaluation

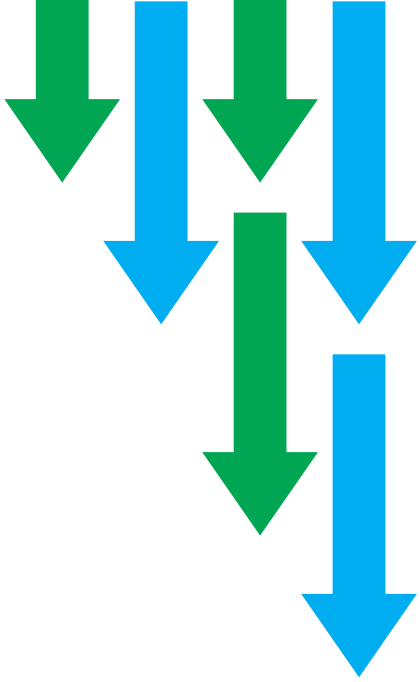
At the end of the event, participants were asked to complete an evaluation survey. Highlights from this evaluation include the following:

- Respondents repeatedly indicated that they liked the diversity of types of stakeholders within the Canadian health system and varying relevant perspectives around the virtual table.
- They appreciated the depth of knowledge of stakeholders and their wide range of expertise. There was confirmation among all that the process needs to be patient-focused.
- Many found the honest dialogue and willingness of stakeholders to collaborate and be solutions-focused very encouraging.
- Many of the respondents saw the importance of learning from one another and not re-creating the wheel but rather leveraging the existing structure for RWE and applying it more broadly.
- Considerations from multi-stakeholders were more complex than initially understood; however, they are not insurmountable.
- Many respondents made a plea for follow-up with the different stakeholder groups after this exchange to ensure that discussions continue and RWE initiatives move forward.

Conclusions

The 2 broad themes that emerged from this robust, multidisciplinary engagement between stakeholders with expertise in data, methodology, clinical practice and research, patient-lived experience, pharmaceutical manufacturing, and policy- and decision-making were centred on collaboration and RWD. The insights gathered at this exchange will form the basis of, and be further explored through, subsequent RWE learning projects aimed at understanding and improving the current portrait of care for rare diseases in Canada.

The in-depth discussion between participants with different perspectives showed there is goodwill and strong interest to work together to gather RWD and generate RWE for decision-making. However, success will require building trust through collaborative relationships and transparent data processes. Further, although there was agreement that multiple stakeholder groups must be involved from the beginning and throughout the collaboration process, participants were unaware of descriptions or guidance about such a multi-stakeholder process. Patients were the most frequently mentioned type of stakeholder and there was agreement among all participants that the process to optimize RWE to support decision-making needs to be patient-focused.



Following the BBE, Health Canada, CIHR, CADTH, and CORD have initiated action to optimize the use of RWE for decision-making about drugs for rare diseases. These groups will collaborate on learning projects through the establishment of an RWE Steering Committee chaired by CADTH and Health Canada. A summary of each of the quarterly meetings of the RWE Steering Committee will be posted on CADTH's new RWE website.

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Appendix 1: BBE Program and Agenda

Table 1: Day 1 BBE Program and Agenda (October 5, 2021)

Agenda item	Presenter/moderator
Opening remarks from chair and co-hosts	· Christopher McMaster · Michelle Boudreau · Durhane Wong-Rieger · Nicole Mittman
Setting the scene	· Karen Facey
Presentation and discussion of fictious case study	· Avram Denburg
Panel discussion: Decision-Maker Needs for Case Study	· Frederic Lavoie, Vice-President, Access and Government Relations, Pfizer Canada, Representing Innovative Medicines Canada · Brent Fraser, Vice-President of Pharmaceutical Reviews, CADTH · Mark Wyatt, Assistant Deputy Minister, Saskatchewan Ministry of Health · Sandra Sirrs, Clinical Professor, Division of Endocrinology and Metabolism, University of British Columbia · Durhane Wong-Rieger, President & CEO, Canadian Organization for Rare Disorders President; CEO, Institute for Optimizing Health Outcomes & Chair, Canadian Heart Patient Alliance
Plenary discussion: Key Gaps Expected in the Evidence Base	· Laurie Lambert · Karen Facey
Breakout group discussions	· Larry Lynd, Director of CORE, University of British Columbia · Kelvin Chan, Medical Oncologist and Associate Scientist, Odette Cancer Centre, Sunnybrook Research Institute · Jean-Eric Tarride, Professor, Health Research Methods, Evidence and Impact, McMaster Chair in Health Technology Management, McMaster University · Mina Tadrous, Assistant Professor, Drug Safety, Health Services Research, Leslie Dan Faculty of Pharmacy, University of Toronto · Tarry Ahuja, Manager, Program Development, CADTH
Feedback	· Laurie Lambert · Karen Facey

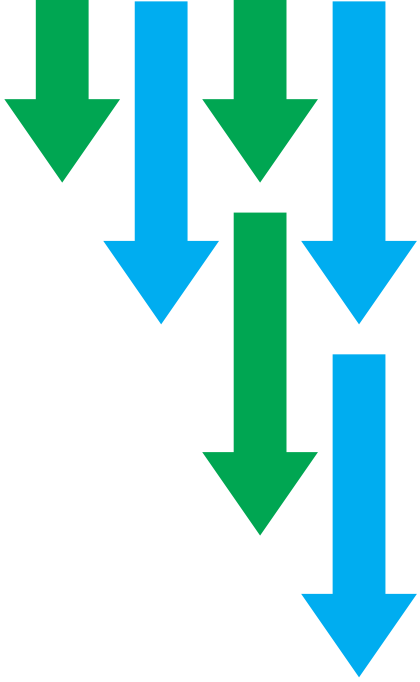


Table 2: Day 2 BBE Program and Agenda (October 6, 2021)

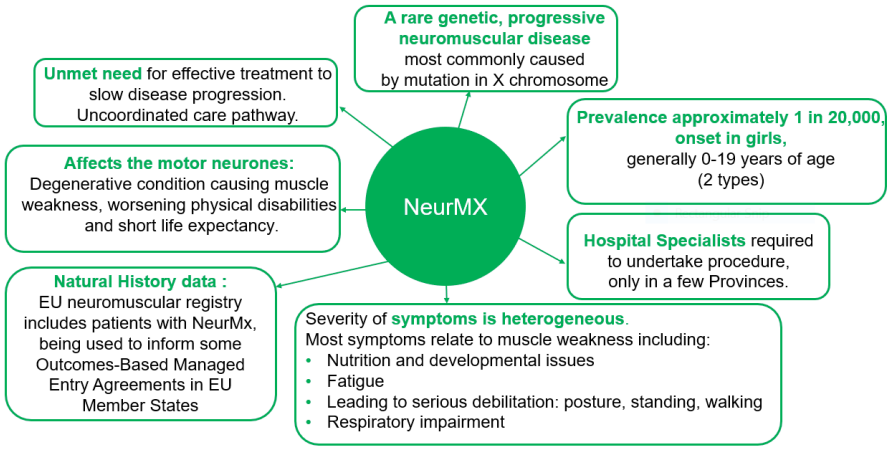
Agenda item	Presenter/moderator
Opening remarks	· Christopher McMaster
Breakout group discussions	· Larry Lynd · Kelvin Chan · Jean-Eric Tarride · Mina Tadrous · Tarry Ahuja
Plenary report back and discussion	· Laurie Lambert · Karen Facey
Panel discussion: Next Steps for Integrating RWE Into Decision-Making	· Nicole Mittmann
Plenary discussion: Key Gaps Expected in the Evidence Base	· Laurie Lambert · Karen Facey
Breakout group discussions	· Frederic Lavoie · Brent Fraser · Mark Wyatt · Sandra Sirrs · Durhane Wong-Rieger
Closing remarks	· Christopher McMaster

Appendix 2: Fictitious Case Study

The fictitious case study presented to BBE attendees was prepared by Dr. Avram Denburg. The case centred on a fictional rare, genetic muscular disease, called NeurMX, and a fictional new drug candidate (Gx) going through an approval process for this indication. The case study included information on NeurMX and the Gx therapy and provided a basis to assess the approval process from an RWE perspective, identify uncertainties, and generate discussion among participants. The case study materials (presented in Figure 5, Table 3, and Table 4) were used to engage discussion around the following questions:

- What RWD should be collected to develop evidence that can resolve the uncertainties for future decisions about whether Gx should continue to be made available and how its use should be optimized (e.g., population to be treated)?
- Where can we get those RWD — from Canada or internationally — and what sources would we trust?
- What would increase our confidence in the results of RWE?

Figure 5: Description of Fictional Disease NeurMX



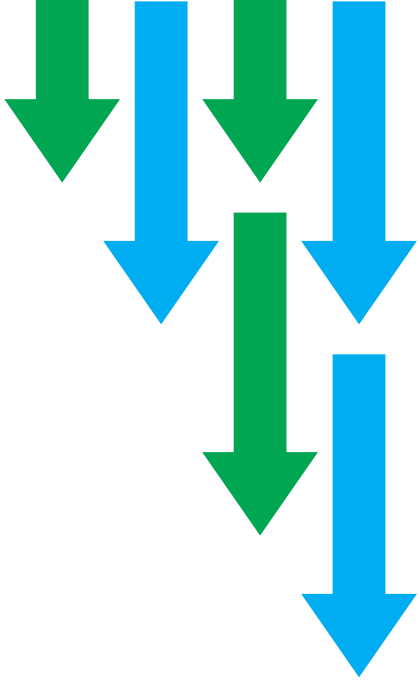


Table 3: Classification of Fictional Disease NeurMX Subtypes

Type	Age of onset	Motor ability and additional features	Survival
Type A	Infants (newborn to 5 years) (~50 in Canada)	· Progressive · Unable to sit, stand, or walk · Respiratory function impaired · Wheelchair by 8 years old · Substantial caregiver burden	Median age of death = 10 years old
Type B	Children and adolescents (5 to 19 years) (~150 in Canada)	· Developmental issues · Unable to walk independently · Respiratory function impaired · Difficulty maintaining weight	Median age of death = 30 years old (with wide variability)

Table 4: Hypothetical Submission of Fictional Drug Gx to Health Canada for Market Authorization (With Conditions)

Detail	Treatment: Gx
Proposed market authorization indication	Treatment of NeurMX disease
Dosage	Nominal 1.0×10^{15} vector genomes vg/kg Gx should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 120 minutes. The total volume is determined by patient body weight. Treatment should be administered in specialist clinical centres.
Price	The list price is $XXXX per vial.
Health Canada conditions expected	Long-term follow-up

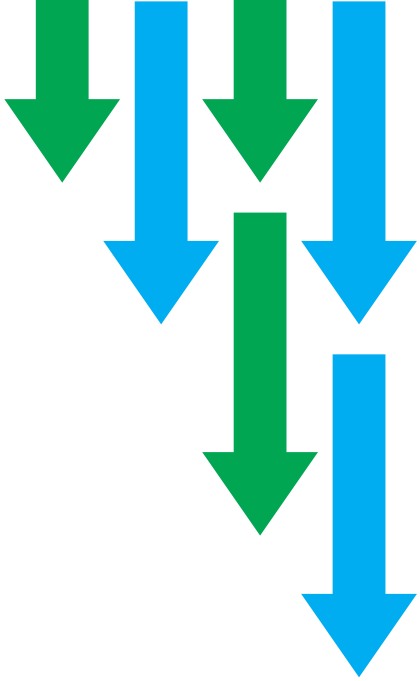
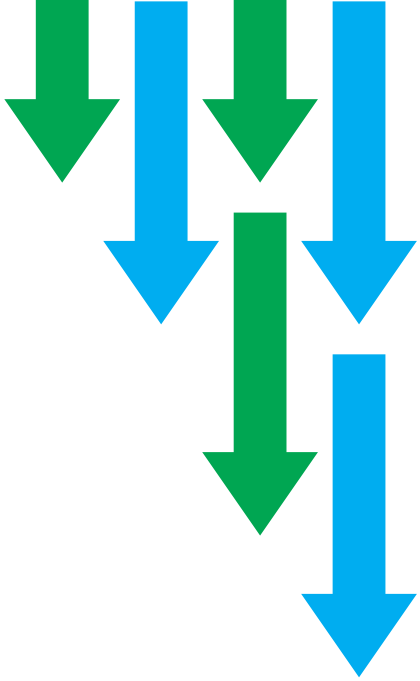


Table 5: Clinical Trial Evidence for Fictional Drug Gx Treating Fictional Disease NeurMX

Detail	Trial 1	Trial 2	Long-term follow-up
Design	Phase II, single US centre, non-comparative N = 20, Gx 2 years follow-up	Phase III, international, multi-centre, non-comparative N = 40 1.5 years follow-up	Long-term follow-up of Trial 1 and Trial 2 For 10 years
Inclusion	Type A NeurMX Adequate hydration and nutrition 1 to 3 years old	Type A NeurMX Adequate hydration and nutrition 6 months to 3 years old	—
Assessments	Quarterly Motor milestones Permanent assisted ventilation Survival All adverse events Caregiver QoL/burden	Quarterly Motor milestones Tube feeding Permanent assisted ventilation Survival All adverse events Caregiver QoL/burden	Annually Motor milestones Permanent assisted ventilation Survival Unexpected adverse events

Table 6: Proposed Control Arm for NeurMX Assessment Including Natural History Evidence

Detail	Natural history
Design	Retrospective chart review – US Registry N = 30 Follow-up at least 3 years
Inclusion	Matching on Type A NeurMX (diagnosis up to 5 years old)
Assessments	Motor milestones Requirement for ventilation Survival (30% died within 3-year follow-up)

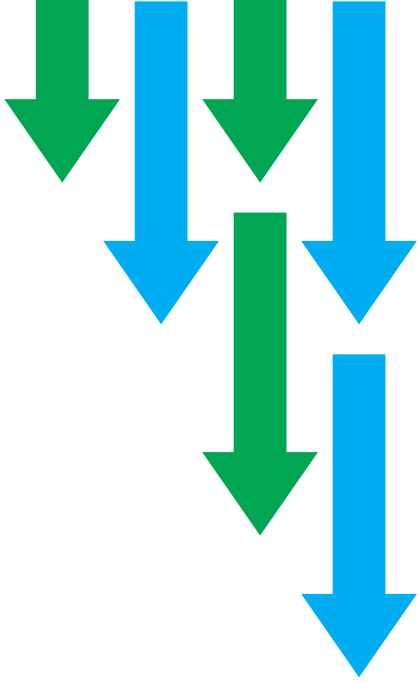


Initial reflections on the case raised the following considerations and uncertainties for the breakout discussions:

- There are many gaps in the types of patients studied, so what should the reimbursed indication be?
- Where should this be used in the care pathway, not just in relation to current treatments, but considering other treatments that may be approved?
- What could the impact of newborn screening be?
- Can natural history be used from jurisdictions outside Canada?
- What is the durability efficacy? Is re-treatment required?
- Long-term safety concerns?
- Can we use RWD from other countries?
- Given the many uncertainties and high price, what payment models could be used?

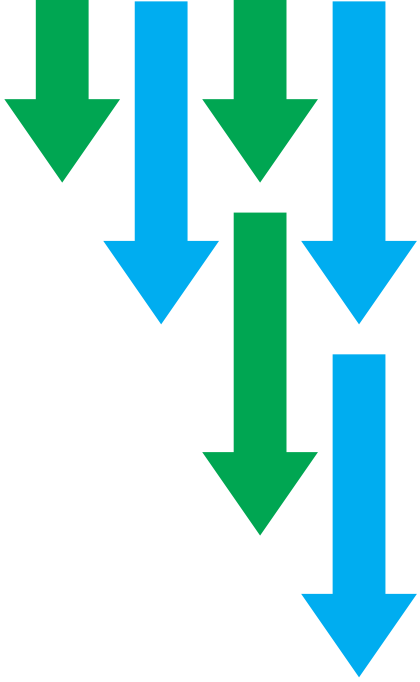
It was noted these patients have no treatment for their condition and the most important evidence gaps to fill are those which measure outcomes that are important to patients.

In a plenary vote, 28% of the audience identified the eligible patient population as the most important uncertainty, this was closely followed by long-term safety/efficacy (26%) and patient quality of life (20%). Functional ability of patients, survival, and natural history in Canada were seen as important by fewer participants (8%, 5%, 4%, respectively). In breakouts, the top 3 topics were discussed alongside the issue of natural history.



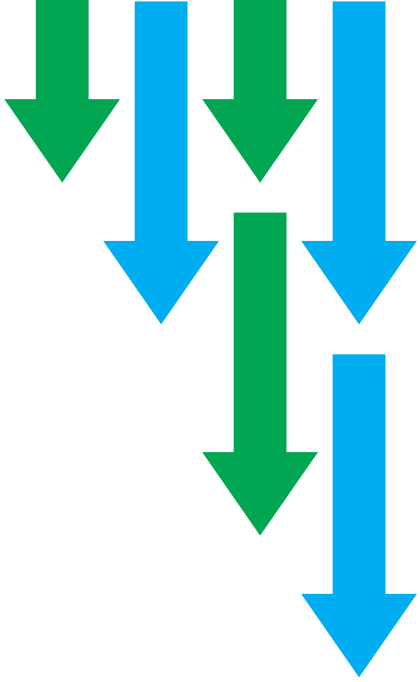
Appendix 3: Qualitative Analysis Using NVivo

- The inductive approach to content analysis (i.e., codes are defined from the data and refined during the data analysis process) was used, as decided through discussion with the analyst and CADTH team.
- The summarized data were imported into NVivo for review and analysis.
- Questions generated during data cleaning and initial reading were tracked and clarified by the CADTH team (e.g., questions about acronyms).
- Memos to track analysis process and progress created.
- Memos to track code development, coding structure, analysis progress from topic identification to themes created and included in the NVivo project.
- All data were read twice before manual coding, then a third time during manual coding. Manual coding was validated and enhanced through documented use of NVivo queries and visualizations.
- Autocoding (for themes and sentiment) was performed as confirmation of codes and themes. Selected examples are included in the Appendix of this report and in the NVivo Project.
- Codebooks were generated to track codes, code descriptions, coding progress, and structure.
- Queries were created to identify frequently used terms and systematically gather coding for those (and related) terms and were included in the NVivo project, as were the query results.
- Visualizations of queries demonstrating frequency (i.e., word clouds) and terms used in context (i.e., word trees) were generated to inform the analysis process.
- Charts were generated to illustrate coding by topic to inform analysis and reporting.
- Maps illustrating initial coding strategy, and thoughts on final coding structure were generated for discussion with the CADTH team.
- Regular discussions with the CADTH team informed the analysis and reporting.



Appendix 4: Discussion Summary for Day 1

- Given the size of Canada's population, for rare diseases with lower prevalence, like the fictitious case, international collaboration will be key.
- Disease registries were considered valuable for a range of purposes, such as understanding the eligible patient population, the natural history of the disease, and outcomes (of those on treatment and those not on treatment). It was highlighted that good quality data collection in registries requires good clinician-patient relationships.
- The value of quality of life and patient experience data was also stressed. In this case of a severe, life-limiting childhood disease, this applies to both the patient and the caregiver. Furthermore, quality of life needs to be considered in relation to the condition per se and the impact of the treatment.
- Early identification of key outcomes needed by all decision-makers is important, and a minimum 5-year period of data collection and integrated mechanisms to support the capture of good quality data should be implemented.
- There were questions about infrastructure, governance, and funding, but also recognition that there is the possibility to learn from the well-established registries.

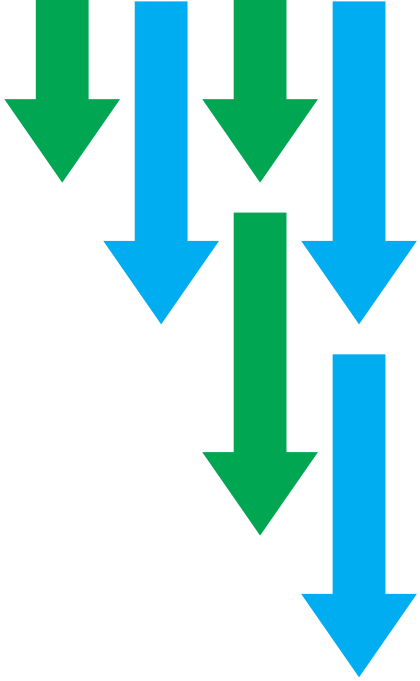


Appendix 5: Discussion Summary for Day 2

Day 2 began in a plenary session with reflections from the facilitators on the key issues for discussion in the breakouts:

- "What is the right way to find the right data to address the crux of the decision-making problem?"
- From day 1, we see a real passion to move forward among all stakeholders and a recognition that Canada has the capacity and expertise to develop RWE prospectively in clinical trials, retrospectively via secondary use of existing data, and in economic modelling.
- We need to consider the infrastructure for linkage of registries, electronic health records, and administrative data across jurisdictions in Canada, with particular consideration given to governance and funding.
- This needs to go beyond "pie in the sky" and we need to create a manifesto for integration of RWE into decision-making. We also need demonstration projects that are realistic and achievable.

In larger group feedback after the breakouts, the importance of clarifying the purpose of RWD collection was emphasized as was the need for earlier dialogues. There is a need to navigate the issues associated with data ownership and create a framework for development of RWE that creates efficiency in data recording so that it is entered once and can be used many times and "does not reinvent the wheel." We need to build collaborations among all stakeholders and learn from well-established national disease registries in Canada and academic excellence in RWD analysis.



Appendix 6: In-Depth Discussion Analysis for the Collaboration Theme

The collaboration theme topics provide detail about participants' perspectives on what is important to consider in collaboration. These topics include participant discussion about key stakeholders and their roles, governance, and the infrastructure required to support stakeholders and decision-makers.

Multi-Stakeholder Dialogue: Who Are the Key Stakeholders and What Are Their Roles?

Points of Consensus

There is goodwill and strong interest to work together to gather RWD and generate RWE for decision-making. Success requires building trust through collaborative relationships and transparent data processes. Although there was agreement that involving multiple stakeholder groups from the beginning and throughout the collaboration process is required, participants were unaware of descriptions or guidance about such a multi-stakeholder process. Patients and patient organizations were the most frequently mentioned stakeholders with additional groups being industry, payers, academics, clinicians, regulators, and HTA agencies. It was also mentioned that further consideration should be given to the inclusion and role of patient caregivers to garner their perspective.

Additional Perspectives

It may be appropriate to involve specific stakeholder groups for specific aspects of the collaborative process, such as industry after trusted relationships have been established, as well as international stakeholders.

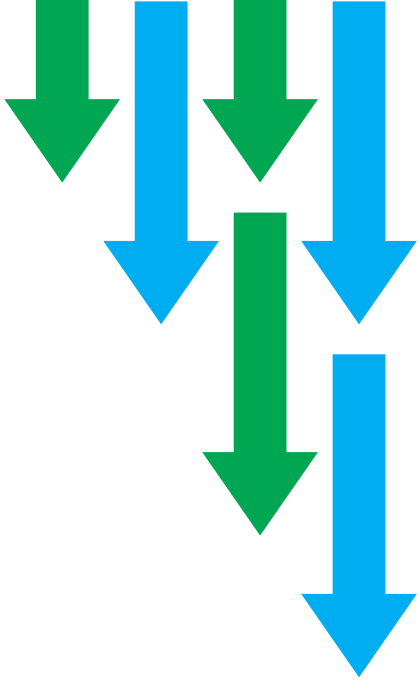
Quotes

The following quotes highlight key principles about the benefits of a multiple stakeholder collaboration among key stakeholder groups, the importance of trust, and how to build relationships:

> "There is an opportunity here for multiple stakeholders to work together to generate high-quality evidence to suit multiple needs, including those of the regulator, industry, HTA, payers, clinicians, etc."

> "Without trust we can't go anywhere."

> "How to collaborate: by understanding more about everyone, having a more honest dialogue, be mindful of competing interests of the stakeholders, be aware of dogma, and how it inhibits collaboration."



Governance: How Will the Stakeholders Work Together?

Points of Consensus

For successful collaboration around RWE is a clear and established governance structure with terms of reference or guidelines that include getting input and feedback from representatives of multi-stakeholder groups. A neutral organization can foster the building of trust by facilitating collaboration and administering the terms of reference. In addition, a neutral organization with expertise in datasets and collaboration could potentially house and govern the data, oversee associated processes and protocols, as well as integrate patients and caregivers into the process.

All aspects of RWD processes and protocols need to be defined, including the purpose of data collection and data elements, ownership, storage, access, analysis, and use. Standards for data analysis must be set by methodological experts and clearly outlined in the governance structure and terms of reference. Roles for each stakeholder group should be defined at the outset, with details communicated throughout the process.

To ensure participation in RWD collection, patients need to understand the purpose and value of RWE and have input into what RWD elements will be collected and how data will be used. Therefore, patient involvement from the outset and throughout data collection and analysis is essential.

Additional Perspectives

The frequency of RWD collection and timelines for reporting of findings should be defined.

Some participants suggested access to rare disease treatments should be contingent on patient participation in data collection via a registry.

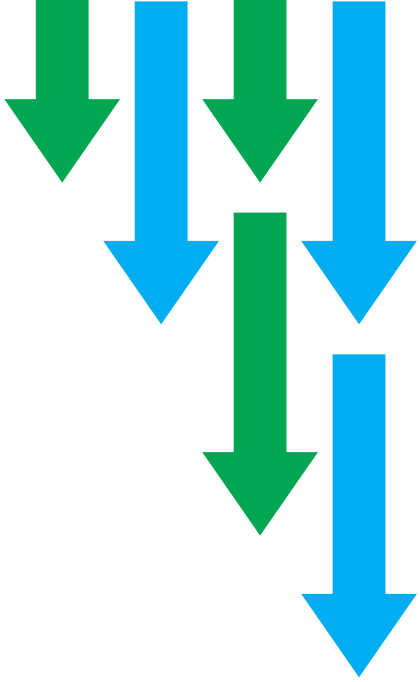
Quotes

The following quote illustrates several key topics raised consistently throughout the collaboration theme, including collaborative multi-stakeholder involvement, the need for a priori agreements, and the desire to have RWD housed by a neutral expert body that would provide oversight:

> "Thinking about real-world evidence in this context for rare diseases, we could have a multi-stakeholder group agree upfront at the time of approvals on what is the minimum outcomes to be studied. And then different groups could do their own studies, or it could be done collaboratively and then pick a body to own the data that is an expert. And then in terms of who could act as the oversight body, it could be CADTH, or another."

The following quote exemplifies the different issues related to RWD for rare disease compared to for RWD and emphasizes the need for agreement and collaboration:

> "There is not a lot of robust data for rare disease and RWE is not structured in the same way as clinical trials so we should consider establishing guidelines for clinicians and evaluators on how we should be analyzing RWE and what level of evidence is acceptable."



Finally, the following quote represents the commonly stated need for a neutral organization and its role:

> "Have one entity (arms-length organization) to manage the collaborations between people which is neutral and have common goals."

Infrastructure: How Will the Work Be Funded?

Points of Consensus

Participants consistently suggested a public private funding model be used given the cost of RWD generation and analysis, with a neutral organization responsible for governance. Ensuring that the RWD is of high quality and meets the information needs of decision-makers will help to demonstrate the value of investing in RWE initiatives.

A national approach to collaboration is the preferred model with the understanding there could be challenges due to different provincial legislation about access to and use of RWD, standards about informed consent and definition and availability of data elements. Ensuring that processes and protocols are clear with the understanding that those who contribute financially or through provision of services have access to the RWD they require. Again, there was interest in international collaboration to share key learnings with similar efforts to collect and use RWE.

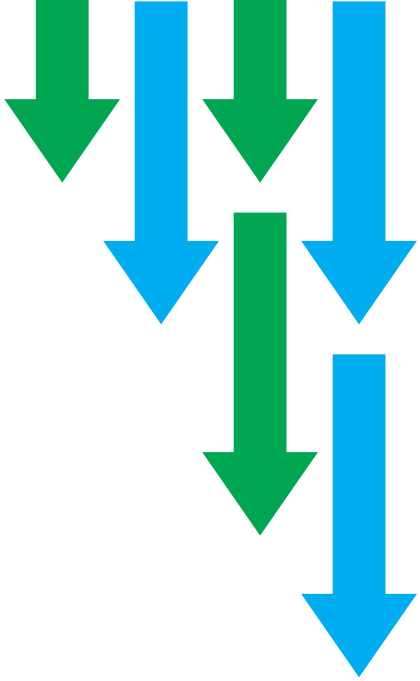
Quotes

The following quote illustrates the benefits of building on existing resources and the potential roles for partners:

> "The cost of the infrastructure for collection, integration, processing, even for providing platforms for collaborative analysis are dropping with the standardization of the processes. The pain points are finding where those data are and gain access, striking those legal agreements, governance, setting standards and figuring out the analysis. They need help from external partners to gain access to those datasets to do analysis and figure out what things can be teased out of the data which is the major cost point."

The following quote describes the benefits of ensuring the cost is aligned to real-world outcomes and the importance of high-quality RWD:

> "We need to be able to attach the cost to real-world outcomes because RWE and outcomes-based agreements can be challenging due to risk from both manufacturers and governments…. Have an eye on subgroups and ensure clear parameters because wrong data can wreck the use of the data. A midcourse correction can be needed to align with a changing environment."



Appendix 7: In-Depth Discussion Analysis for RWD Theme

The topics identified in the RWD theme concern participant discussion of what RWD to collect, where to get the RWD (RWD sources), and how to analyze it. In addition, considerations about how to increase confidence in the RWD and its gaps and limitations are presented.

What RWD to Collect to Resolve Uncertainties

Points of Consensus

Building a natural history dataset takes time to establish and to accumulate sufficient information to be useful, especially for rare diseases. Therefore, planning should begin as early as possible. These datasets could be used for comparison (natural history of disease versus treatment) and for the collection of data elements that may not be of immediate interest but may emerge as important as treatments evolve.

Multidisciplinary stakeholder alignment and agreement on data elements for collection should be determined a priori. To ensure consideration of the context for Canadian data users and decision-makers, Canadian-specific RWD should be captured.

Examples of end points include, but are not limited to:

- disease-based outcomes (severity of disease, disease stabilization, or progression)
- treatment outcomes (adverse events, safety data, additional medications)
- comparative outcomes (natural history, control groups, treated patients not included in trials)
- quality of life, with standardized measures
- patient-reported outcomes
- economic outcomes (health care resource utilization, cost-effectiveness, cost-utility, direct and indirect costs to patients/families)
- epidemiology for the Canadian context (incidence, prevalence, burden of disease)
- identifiable patient-level RWD that can be linked with other RWD sources.

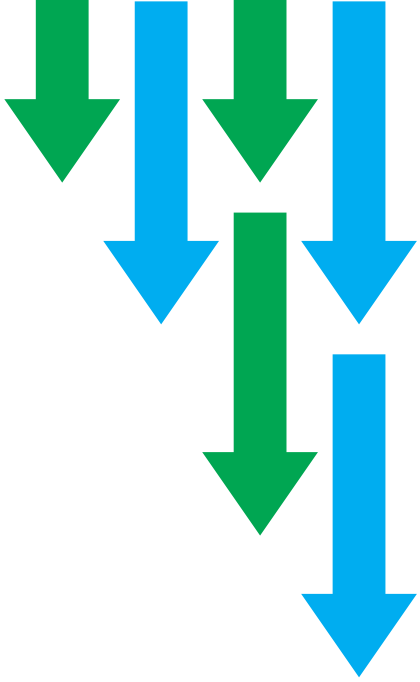
Additional Perspectives

The importance of caregiver-specific data and the relevance of surrogate measures was highlighted. Further, cost-effectiveness analysis in the context of uncertainty could be pursued using the multi-criterial decision analysis approach.

Where to Get the RWD (RWD Sources)

Points of Consensus

Sources of RWD are highly varied and contain many different types of data and different qualities of data (e.g., health care resource utilization data, claims data, industry lead data, administrative data, electronic medical records or chart reviews, hospital data, manufacturer data, natural history studies). Drug- or disease-specific registries also provide a source of RWD, and both Canadian and international registries could be used to augment other types of data, such as outcomes from administrative



datasets. Regarding establishing infrastructure for a national-level rare disease registry, 2 options were discussed: a single national-level rare disease registry with both common and disease-specific data elements and a national-level platform in which disease-specific registries could be combined. It was suggested to include mandatory reporting for rare diseases regardless of the chosen option.

Additional Perspectives

Administrative data alone should not be used due to its limitations.

Quote

The following quote illustrates the benefits of working across jurisdictions to increase sample size:

> "Data needs to be used to its full potential. In Canada and especially with rare diseases, we need to make sure of obtaining the full sample size across jurisdictions; this will require the political will to get there and starting upstream to ensure data holdings are designed in a way that they can be linked with administrative data that are routinely collected."

RWD Quality: What Would Increase Confidence in RWD?

Points of Consensus

Defining the requirements of high-quality RWD is essential from the outset and should involve input from a multi-stakeholder panel. An independent review of RWD quality and the inclusion of early warning signals concerning safety will enhance confidence in RWD collection. Opportunities for prospective generation of RWD should be considered for comparison of Canadian-specific data with international data with the caveat that the health care context and systems can vary widely.

Quote

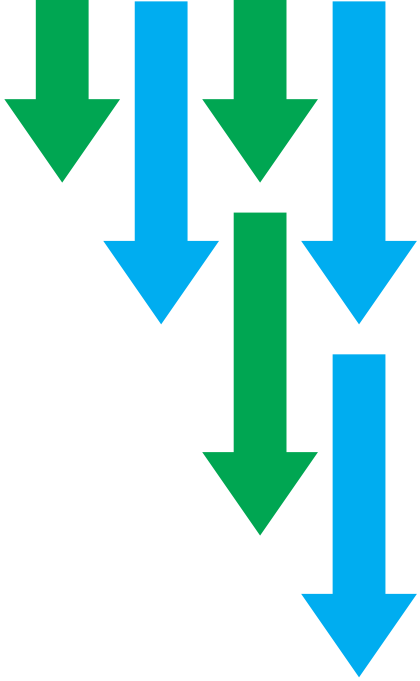
> "It is critical that, a multi-stakeholder team comes together right at the inception of the design to say what kind of data is needed and what are going to be the caveats around the quality of that data."

RWD Gaps and Limitations: What Are the Gaps and Limitations of Current and Potential Datasets?

Points of Consensus

In the area of rare diseases, there is often limited RWD available. An investment of time and other resources is required to build datasets, often in collaboration with international groups. Sometimes there is missing data within registries, particularly information about:

- administration of treatments for compassionate reasons
- a comparison group
- treatments through special access programs
- specific subgroups of patients, such as those with hepatitis C and indigenous populations.

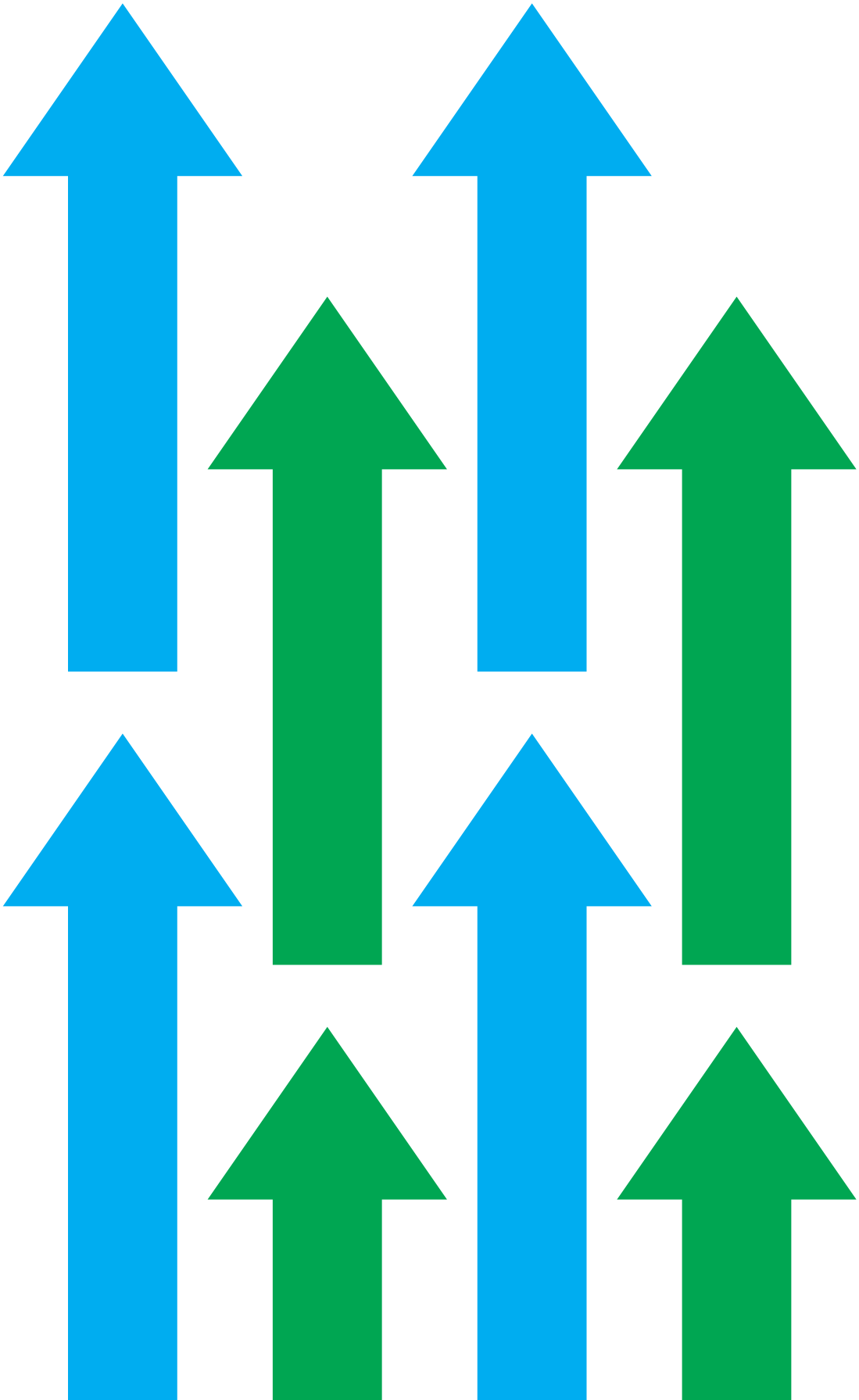


Missing RWD is often retrieved retrospectively via paper chart review, and this can be a limitation to the quality of the data.

Obtaining ethics approvals across jurisdictions also can be a barrier for effective and efficient data collection and analysis.

Additional Perspectives

Data collection for some patient health variables requires training of clinical staff to understand and apply measurement tools to measure signs, symptoms, and treatment response. Health care resource and safety data are also often difficult to capture and retrieve from datasets.



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