Integration of Real World-Evidence (RWE) into Regulatory Decision-making - Health Canada's Perspective

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Overview

- Background
  - Definitions Real-world data (RWD)/real-world evidence (RWE)
  - Regulatory Review of Drugs and Devices
- Use of RWE at Health Canada
- Key collaborations in RWE
  - Domestic
  - International
- Opportunities and Challenges
- Considerations

Part 1 - Background

Definitions of Real-World Evidence

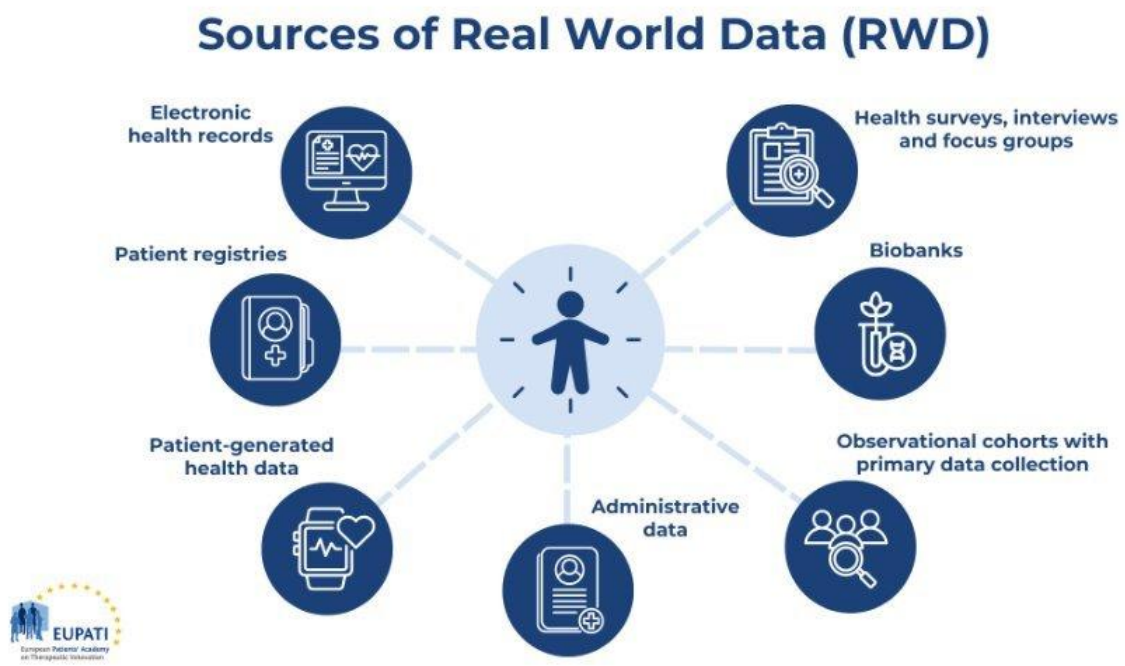
Real-World Data (RWD): data related to patient health status and/or the delivery of health care that are routinely collected from various real-world sources (e.g., electronic health records, administrative claims, disease registries, etc.).

Real World Evidence (RWE): the clinical evidence regarding the usage and potential benefits/risks of a product derived from the analysis of RWD.

RWE studies complement sources such as spontaneous adverse event reports and randomized clinical trials (RCT) by providing insights into drug benefit–risk profiles in real-world clinical settings

https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html

Real-World Evidence (RWE)



Strengths:

Larger sample size
Longer follow-up
Greater generalizability
Fewer resources

Limitations:

Not fit-for-purpose
Data Quality (e.g., Confounding/Bias)

https://toolbox.eupati.eu/resources/patient-toolbox/real-world-data-rwd-real-world-evidence-rwe/

How RWE Strengthens Drug Regulatory Decision-Making and Access

👥 Regulatory Decision-Making

- Complement clinical trials
- Benefit–risk under uncertainty
- Support conditional approvals

⚡ Access & Coordination

- Align with Health Technology Assessment (HTA) bodies/provinces
- Improve access in rare diseases
- Reduce evidence gaps

📊 Lifecycle & RWE Integration

- Continuous evidence generation
- Post-market monitoring and timely risk communication
- Adaptive regulation

Enablers:
Guidance
Data standards
Partnerships
Transparency

Regulatory Review of Drugs and Devices (R2D2)

- Launched in 2017 by Health Canada (HC) to improve/modernize Canada's regulatory system for health products
- Implementation involved 10 initiatives supported by 14 projects (2017-2022)

Expanded Collaboration With Health Partners

- Alignment of HTA Review with Health Canada
- Use of foreign regulatory reviews
- Increased international collaboration

More Timely Access to Drugs

- Expansion of priority review pathways
- Improved access to biosimilars & generics
- Enhanced pathways for digital health
- Pre-submission advice

Enhanced Use of Real-World Evidence

- Use of RWD for assessing safety & effectiveness
- Integration of RWE in decisions
- Strengthening RWE frameworks across produce life-cycle

Modern and Flexible Operations:
Common submission intake |Appropriate Cost recovery framework | Public release of clinical information

Key R2D2 Achievements

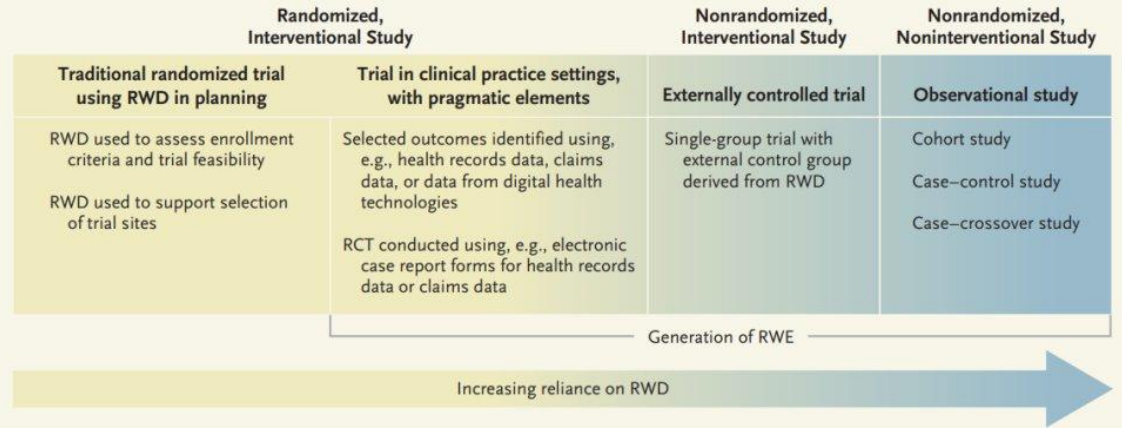
- Consulted health partners to identify existing data sources
- Established Drug RWE Steering Committee with Canada's Drug Agency (CDA)
- Co-developed CDA guidance for transparent RWE reporting and use
- Published Health Canada position on CDA guidance
- Issued notice on Optimizing RWE For Regulatory Decision-making
  - Elements of RWD/RWE Quality throughout the Prescription Drug Product Lifecycle
- Participated in international RWE collaborations
- Supported international harmonization to accelerate access to specialized therapies

Part 2 - Use of RWE at Health Canada in the Post-Marketed Space

HC Use of RWE for Regulatory Decision-Making

HC recognizes the value of high-quality RWD/RWE, particularly for:

- Underrepresented populations (e.g., children, older adults, pregnant individuals)
- Rare diseases where clinical trials may be infeasible
- Public health emergencies where clinical trials may be unethical or impractical



Concato, J., Corrigan-Curay, J., & Real-World Evidence Subcommittee. (2022). *Real-world evidence — Where are we now? New England Journal of Medicine, 386*(18), 1680–1682. https://doi.org/10.1056/NEJMp2203089

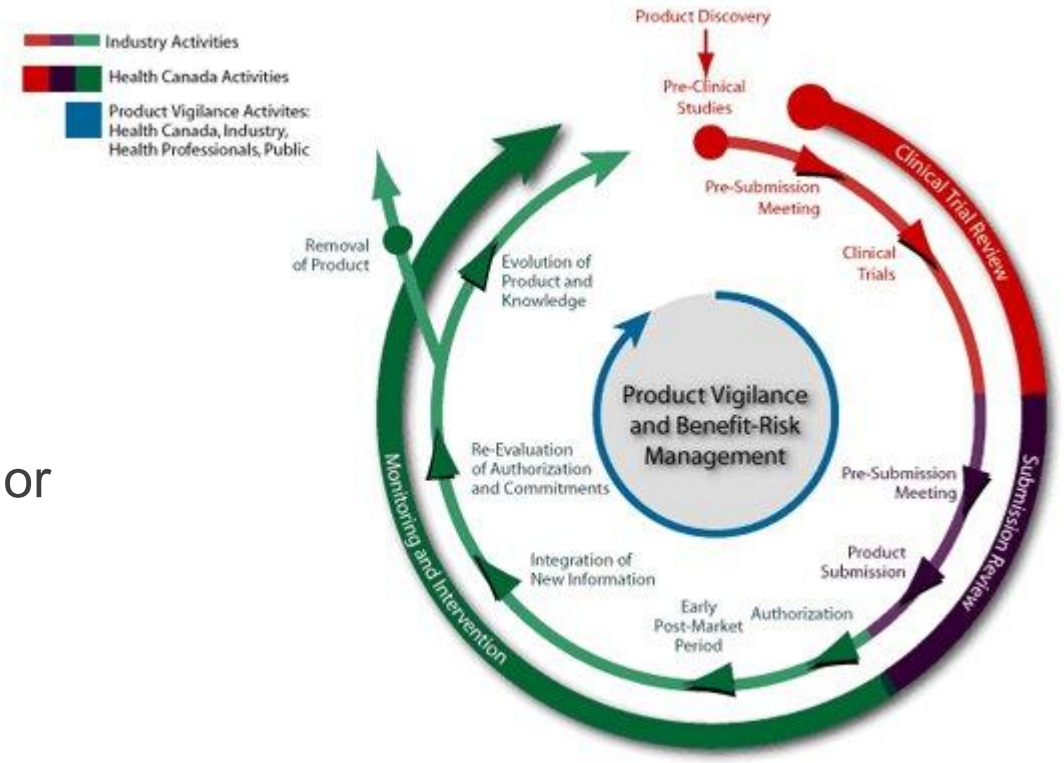
Integration of high-quality RWE is encouraged in:

- Pre- and post-market drug evaluations;
- Notice of Compliance with Conditions (NOCc) pathways;
- Orphan drug reviews

HC Use of RWE Across Product Life Cycle for Regulatory Decision-Making

Pre-market: RWE is considered as part of totality of evidence in pre-market drug packages

Post-market: RWE is often used in signal detection or to inform pharmacovigilance and risk management



RWE at Health Canada - Pre-Market Activities

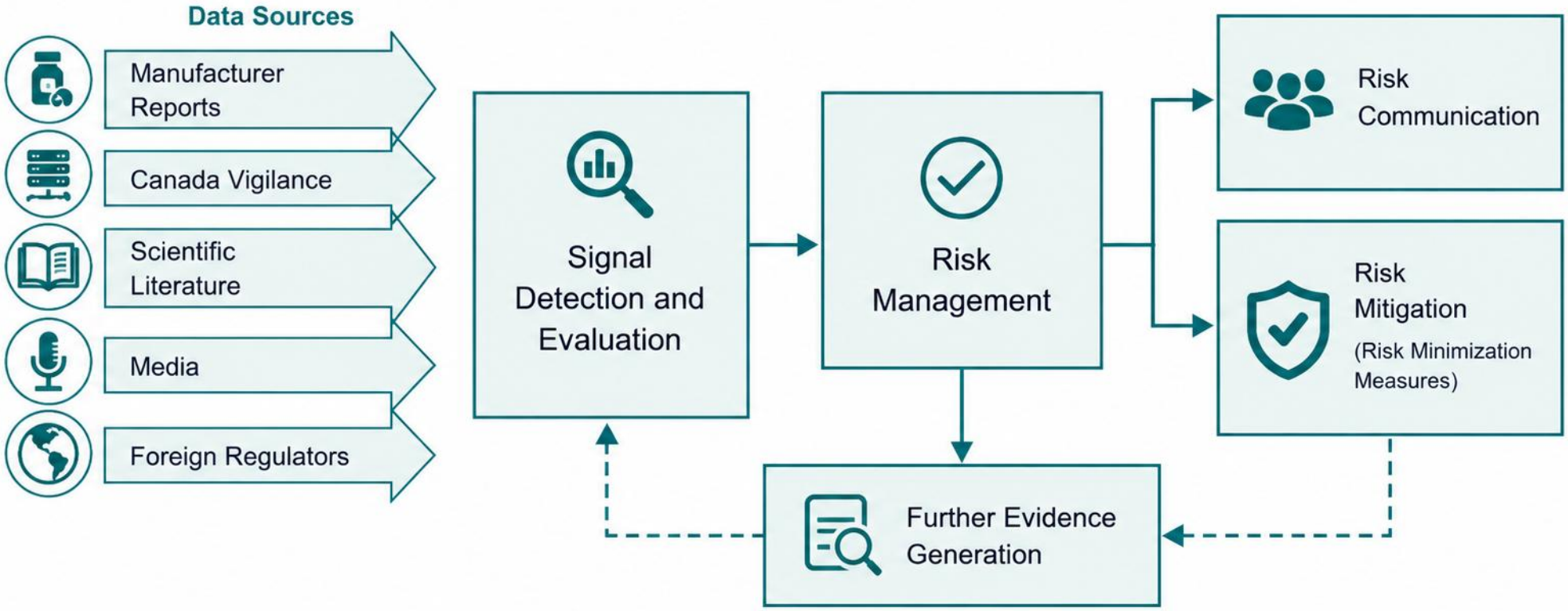
Supplemental: As part of totality of evidence in pre-market drug packages; RWE is accepted to support efficacy and safety, especially when traditional trials are challenging or unethical.

Indications Expansion: RWE is used to expand evidence-based indications for populations typically excluded from trials, such as children, older adults, and pregnant women.

Scientific Advice: Through joint initiatives with CDA, early engagement allows sponsors to align RWE generation plans with regulatory needs.

RWE at Health Canada - Post-Market Activities

Post-Market Monitoring and Evaluation: RWE plays a significant role in ongoing safety monitoring and managing post-marketing obligations through stakeholder engagement, evidence evaluation, and evidence generation.



Part 3 - Key collaborations in RWE

Canada's Collaborative Approach to RWE

Collaboration in RWD/RWE	• To address challenges in the RWD/RWE landscape, Canada collaborates with domestic and international partners to enhance harmonization, strengthen methodologies, and support evidence generation.
International collaborations are of key importance	• International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (**ICH**); European Medicine Agency (**EMA**); International Coalition of Medicines Regulatory Authorities (**ICMRA**); international clusters involving Food and Drug Administration (**FDA**)
Knowledge Sharing and Stakeholder Engagement	• Presenting regulatory perspectives and RWE experience at national and international conferences and stakeholder forums across pre- and post-market settings

HC Domestic RWE Collaborations

HC collaborates with a variety of **domestic partners** to improve the use of RWE (e.g., patient group consultations, Health Technology Assessment partners, payers, professional associations, academia)

Key Domestic Collaborators

- CDA
- INESSS
- PHAC
- Industry Partners
- Clinical & research institutions
- P/T Health Systems
- HTA bodies
- Patient Groups

INESSS - Institut national d'excellence en santé et en services sociaux
PHAC – Public Health Agency of Canada
P/T – Provinces and Territoires

Examples of domestic collaborative activities:

- Drug RWE Steering Committee
- Guidance for Reporting Real-World Evidence
- Pan-Canadian CoLab Network
- The National Strategy for Drugs for Rare Diseases
- Pediatric Drug Action Plan
- **HC PMDE Program**

CoLab

Canada's Drug and Health Technology Agency
L'Agence des médicaments et des technologies de la santé au Canada

In collaboration with / En collaboration avec
Health Canada Santé Canada

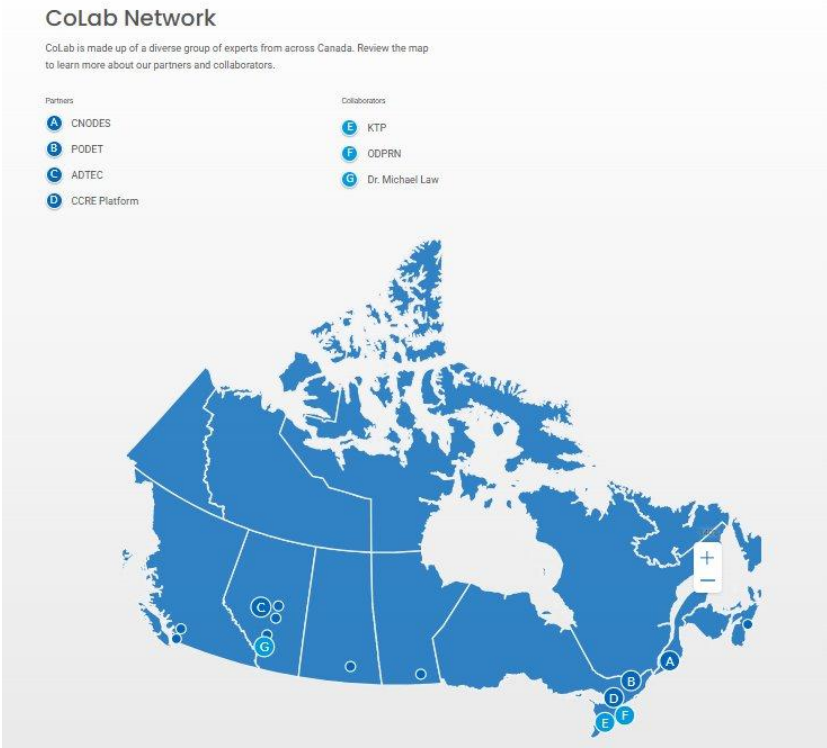
Guidance for Reporting
Real-World Evidence
May 2023

RareKids CAN

Post Market Drug Evaluation (PMDE) Program

PMDE is the unified, coordinated pan-Canadian system for generating RWE to support drug safety, effectiveness, and policy decisions in Canada

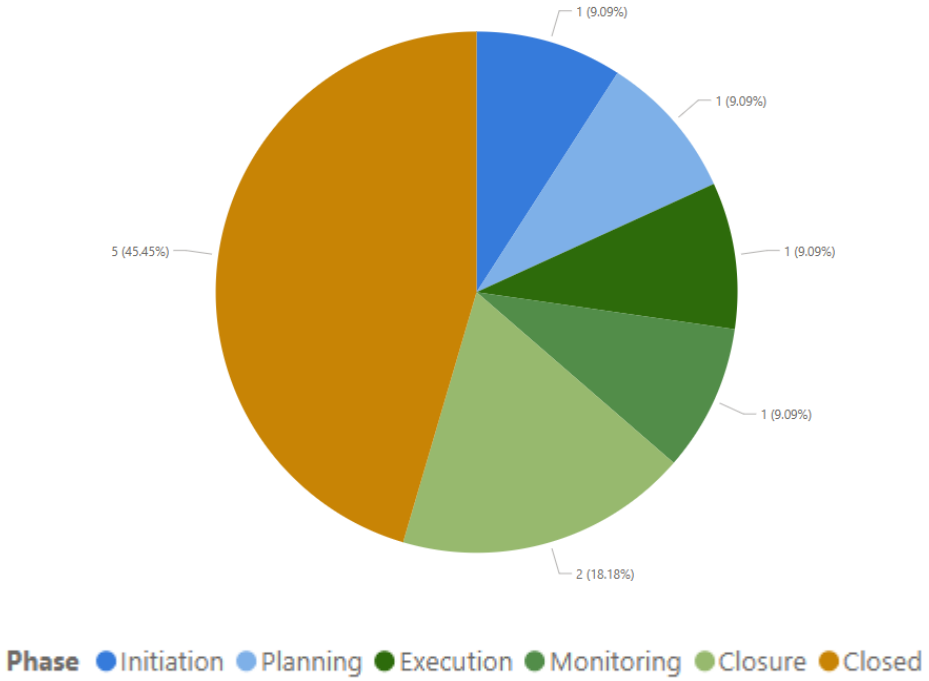
- CDA initiative funded by HC
- Provides timely, methodologically rigorous evidence for decision-makers
- Works with a pan-Canadian CoLab Network of research experts
- Uses RWD and advanced methods to support decision-making

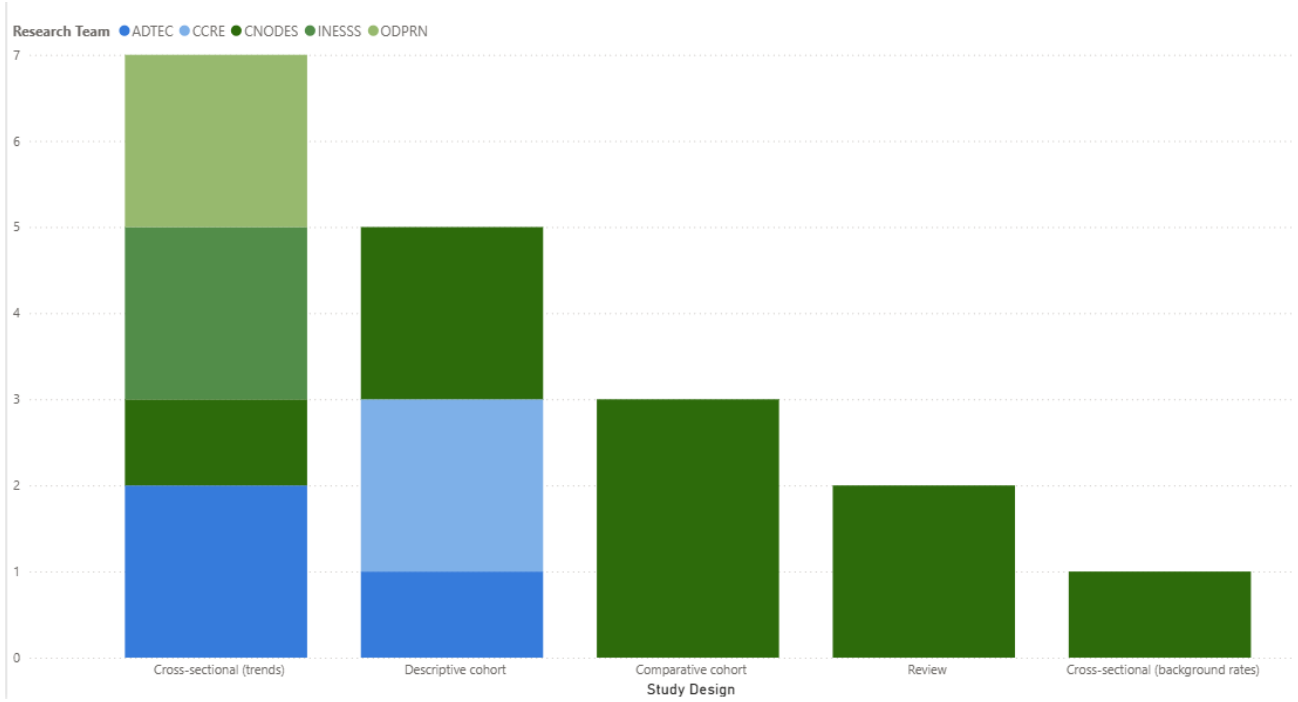


HC's Drug Evidence Appraisal and Management (DrEAM) Office: serves as the liaison for PMDE queries, coordinating submissions, managing project workflows, reviewing documentation, and offering epidemiological expertise for requestors.

Post Market Drug Evaluation (PMDE) Program

Evidence generation: enables HC to proactively initiate queries that address safety evidence gaps and support exploration of innovative RWE methodology





HC International RWE Collaborations

- International Coalition of Medicines Regulatory Authorities (**ICMRA**) working groups
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (**ICH**)
- European Medicines Agency (**EMA**)
- **RWE International Clusters** - FDA/HC/EMA RWE Cluster meetings

Transparency

Harmonization of terminologies for RWD/RWE

Readiness to address public health challenges and emerging health threats

Regulatory convergence on RWD/RWE guidance and best practices

ICMRA COVID-19 and Observational Studies WG

- Established in April 2020, and co-chaired by HC and EMA to facilitate international collaboration and generate RWE on COVID-19 treatments, outcome and epidemiology
- Fostered new collaborations for observational studies, facilitated data sharing, and promoted global knowledge exchange
- Three technical workstreams:
  - The Vaccine Pharmacovigilance Network led Medicines and Healthcare products Regulatory Agency (MHRA) and Therapeutic and Goods Administration (TGA),
  - Pregnancy observational research (led by EMA), and
  - The development of international COVID-19 patient cohorts (led by HC)
- Officially closed in February 2024
- **Key outcomes**: new collaborations, enhanced data sharing, joint publications
  - Collaborative RWE Among Regulators: Lessons and Perspectives – 2025
  - ICMRA statement promoting the global use of RWE

ICMRA RWE Working Group for Public Health Emergencies (PHEs) Preparedness

- ICMRA COVID-19 and Observational Studies WG reorganized in 2024 to expand focus on RWE for PHE preparedness
- Supports international collaboration on RWD/RWE for public health emergency preparedness
- First meeting in July 2024 - 16 international regulatory agencies and WHO
- HC is currently an active member and contributes to two ongoing international observational studies:
  - **Background Rates of Adverse Events of Special Interest (BGRs of AESI) for Vaccine Safety Signal Evaluations:** Examining the baseline rates for AESI to improve signal detection and interpretation in vaccine safety monitoring.
  - **GLP-1 RA Utilisation and Drug Shortages:** Examining utilization patterns of GLP-1 receptor agonists and the impact of shortages on patient care and treatment continuity.

EMA/FDA/HC RWE Cluster

- Health Canada joined in 2019, monthly forum to discuss RWE topics
- Supports alignment of regulatory approaches, information sharing, harmonized standards, and sharing of best practices
- Advances emerging methodologies for RWE use in drug approvals and post-market evaluations, enabling faster evidence-based international decision-making

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

ICH develops harmonized guidelines for pharmaceutical regulation, including RWE standards, with contributions from HC to advance international RWE approaches in pharmacovigilance.

- ICH Reflection Paper on International Harmonisation of RWE - Advances global alignment on RWE methodologies, terminology, and reporting principles
- ICH E23: Considerations for the Use of RWE to Inform Regulatory Decision Making with a Focus on Effectiveness of Medicines - Provides considerations for using RWE to assess medicine effectiveness
- ICH M14: General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines - Establishes principles for RWD-based safety studies and post-market assessments

European Medicines Agency (EMA)

HC collaborated with the EMA on RWD/RWE initiatives to advance regulatory acceptance of RWD/RWE for rare diseases, Alzheimer's disease, and pandemic response

- EMA/HMA Big Data Steering Group Workshops - Collaborated with international stakeholders on RWE methodologies and regulatory applications
- Patient Registries for Alzheimer's disease - Supported alignment on registry governance, core data elements, and interoperability for global RWE generation
- **Fitness-for-Purpose Projects:** Worked through ICH and ICMRA to assess whether RWD sources are suitable for regulatory decision-making
- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (**ENCePP):** Participated in the ENCePP Steering Group to support international pharmacoepidemiology and pharmacovigilance initiatives

Use of RWE Across Product Life Cycle for Regulatory Decision-Making

Challenges

- Data may be incomplete, or not fit-for-purpose
- Data quality can be variable or poor
- Repurposed data may not capture desired variables or endpoints
- Significant methodological challenges in converting RWD into reliable RWE
- Requires detailed understanding of data structure, endpoints, and timing
- Continuous access to multiple databases may increase risk of type I error
- Assumptions required for causal inference are not always met

Opportunities

- Often readily available and accessible
- Enables more timely evidence generation
- Includes large and diverse patient populations
- Strong external validity due to representation of real-world clinical practice
- Captures outcomes across broader patient groups than traditional trials
- Quality and reliability of RWD sources continue to improve over time

What Does This All Mean for Regulatory Professionals?

- RWE is increasingly being used as complementary evidence to support regulatory decision-making across the drug product life cycle
- Regulatory professionals should be prepared to assess the quality, relevance, and fit-for-purpose nature of RWD/RWE used in submissions and post-market activities
- The growing availability of health care data highlights the importance of robust evidence evaluation, data governance, and methodological rigor
- Continued alignment with evolving Health Canada and international RWE initiatives will be important to support regulatory convergence and harmonized approaches
- Cross-functional collaboration and stakeholder engagement will remain essential to support efficient evidence generation and informed regulatory decision-making

Thank you

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ANNEX: Key HC Resources for the Use of RWE for Regulatory Framework

- HC's Notice on Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making
- Elements of RWE/D Quality throughout the Prescription Drug Product Life Cycle
  - Provides overarching principles for RWE generation, key considerations for protocol development, and data quality considerations for RWE submissions.
- CDA Guidance for Reporting Real-World Evidence
  - Principles for the use and transparent reporting of RWE in regulatory and HTA decision-making in Canada.
  - Developed in collaboration with Canada's Drug Agency (formerly CADTH) and the pan-Canadian RWE Steering Committee.
- Health Canada's position on the CADTH Guidance for Reporting RWE to Support Decision-making
  - Outlines Health Canada's approach to using and transparently reporting high-quality RWE to support regulatory and HTA decision-making in Canada.