

#RARE
DISEASE
DAY

APR 29 - 30, 2025

Rare Disease Day 2025 Conference



Canadian Organization
for Rare Disorders

WESTIN CALGARY DOWNTOWN
320 4 AVE SW Calgary, AB



ALL ABOUT DATA

International Initiatives on RWD/RWE from Drug Development to Real-World Monitoring

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Outline and Disclaimer



- Setting the scene on opportunities from data and challenges in RDs
- Some International initiatives to face current and future challenges
- Final reflections

The opinions expressed in this presentation are only mine and shouldn't be attributed to anyone else, neither represents a company position

The opportunity from data is enormous...



Data is information collected through observation (RWD) or experimentation

From a developer perspective, there are 2 reasons to analyze data; one is **to understand the underlying mechanisms that drive the things we observe**, and the other is to use whatever analysis we've arrived at, **to do prediction**.

Prediction with what purpose?

- To face future / competitive challenges by getting faster, and **stronger scientific evidence**.

- Improving epidemiology data and NHD.
- Refine hypothesis and research questions
- Understand feasibility of studies
- Fine tune study design
- Better characterize population and diseases. Disease modeling
- Improve patient recruitment, retention and reduce trial times.
- To better, cheaper and faster estimate efficacy, safety (long term ambition), comparative effective comparative long term safety.
- Risk monitoring
- Help incorporating patient subgroup identification in clinical development

- To better capture **Patient Relevant Outcomes**.

- To facilitate decisions for **early access and reassessment from evidence assessors**.



Real-World Data, Real-World Evidence and Real-World Insights



The collection of real- world **data** underpins **evidence** generation, that derives in real-world **insights** which are the actionable conclusions.

Insights from evidence influences regulatory, HTA and reimbursement decisions, clinical practices, and policy-making

Insights should be the result careful **interpretation and analysis of evidence**, transforming raw data into meaningful information



Image from Qlik



Real-World Data, Real-World Evidence and Real-World Insights: Main challenges in RDs

Interpretation and analysis of evidence, the named **the quality of evidence**, is the main challenge in RDs with the use of evidence assessment frameworks (EAF) that were build upon to analyze evidence from prevalent conditions

Evidence from rare **ALWAYS graded low quality** and high uncertainty. This pejorative terminology is **used as insight for decision making**

Health Policy Analysis

Use of Real-World Evidence in Health Technology Reassessments Across 6 Health Technology Assessment Agencies

Ashley Jaks, MPH, Patrick Joseph Arena, PhD, Melinda Hanisch, MIA, Mark Marsico, PhD

ABSTRACT

Objectives: To review health technology assessment reassessments (HTARs) and characterize the use of real-world evidence (RWE) in HTARs.

Methods: Six agencies were chosen for inclusion in this targeted review: Canadian Agency for Drugs and Technologies in Health, National Institute for Health and Care Excellence, Haute Autorité de Santé, Gemeinsamer Bundesausschuss/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Zorginstituut Nederland, and Pharmaceutical Benefits Advisory Committee. Each agency's assessment was screened to identify their 8 most recent HTARs, which were evaluated to determine if they used RWE. If for a given agency less than half of the screened HTARs used RWE, we identified an additional 4 HTARs for evaluation. For each reassessment, we extracted drug characteristics, HTAR details, initial assessment details, and if/how the RWE was used. Narrative synthesis in conjunction with descriptive statistics were used to characterize the findings.

Results: We identified 40 HTARs across the agencies. Over half of the HTARs were for oncology therapies. Additionally, 55% used RWE; these reassessments tended to be for orphan therapies. RWE was submitted to address at least 1 clinical uncertainty, with the most common being related to the primary/secondary endpoints. The majority of RWE studies came from registry data (57.1%). Moreover, the proportion of HTARs resulting in no change in patient access was similar between HTARs that did and did not use RWE. Lastly, no de novo RWE comparative effectiveness studies were identified.

Conclusions: Our findings imply that RWE can play a role in addressing uncertainties identified at launch, especially in addition to clinical trial evidence; agencies and sponsors should collaborate align on evidence needs and study feasibility to ensure RWE can be effectively used in reassessments.

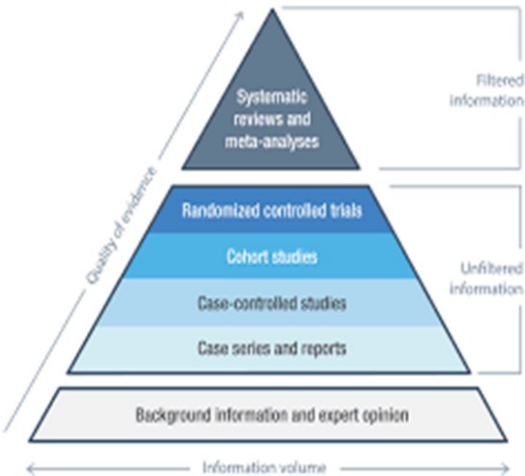
Keywords: health technology assessment, lifecycle management, real-world data, real-world evidence, reassessment.

VALUE HEALTH 2025; ■■■■

Highlights

- Previous studies have highlighted that many health technology assessment (HTA) agencies have developed health technology assessment reassessment (HTAR) processes to move toward a lifecycle approach to HTA and that payers believe that real-world evidence (RWE) should play an important role in HTARs. However, these studies also underscore the limited research on how often RWE is submitted and how RWE is used in HTAR decisions.

- This article shows how RWE can be used in several therapeutic areas (eg, oncology and cardiovascular disease) to address a variety of uncertainties identified at launch, such as those related to adverse events/safety, primary and secondary effectiveness/efficacy endpoints, and treatment utilization. Moreover, this study demonstrates that RWE has mainly complemented clinical trial evidence for addressing clinical uncertainties.



GRADE: what is “quality of evidence” and why is it important to clinicians?

Guideline developers use a bewildering variety of systems to rate the quality of the evidence underlying their recommendations. Some are facile, some confused, and others sophisticated but complex.

In 2004 the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group presented its initial proposal for patient management.¹ In this second of a series of five articles focusing on the GRADE approach to developing and presenting recommendations we show how GRADE has built on previous systems to create a highly structured, transparent, and informative system for rating quality of evidence.

A guideline's formulation should include a clear question
Any question addressing clinical management has four components: patients, an intervention, a comparison, and the outcomes of interest.² For example, consider the following: in patients with pancreatic carcinoma undergoing surgery, what is the impact of a modified resection that preserves the pylorus compared with a standard wide tumour resection—variations of the Whipple procedure—on short term and long term mortality, blood transfusions, life leaks, hospital stay, and problems with gastric emptying?

Guideline developers should address the importance of their outcomes
GRADE challenges guideline developers to specify all outcomes that are of importance to patients as they begin the guideline development process, and to differentiate the critical outcomes from the non-critical ones.³ Figure 1 presents a hierarchy of patient important outcomes regarding the impact of phosphate lowering drugs in patients with renal failure. GRADE suggests a nine point scale to judge importance. The upper end of the scale, 7 to 9, identifies outcomes of critical importance for decision making. Ratings of 4 to 6 represent outcomes that are important but not critical. Ratings of 1 to 3 are terms of limited importance. Guideline panels should strive for the sort of explicit approach that this example represents.

Five limitations can reduce the quality of the evidence
The GRADE approach involves making separate ratings for the quality of evidence for each patient important outcome and identifies five factors that can lower the quality of the evidence (see box).⁴ These factors can

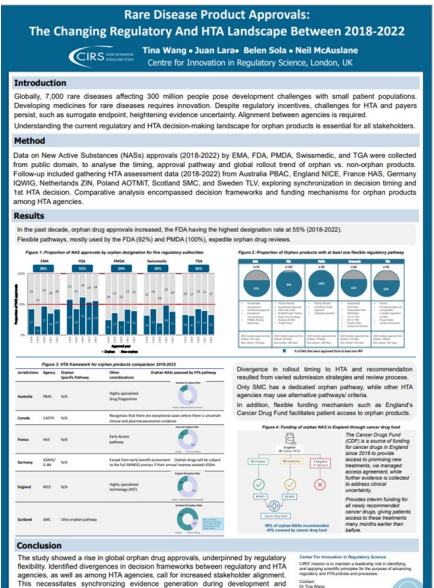


Fig 1 Hierarchy of outcomes according to importance to patients to assess effect of phosphate lowering drugs in patients with renal failure and hypophosphatemia

Potential solutions: Changing the paradigm



Operationalize the concept: **Totality of Evidence for Rare diseases** isn't Low Quality



A banner for the Rare Disease Day 2025 Conference. The text is white and set against a background of teal and purple brushstrokes. The text reads: "Rare Disease Day 2025 Conference April 29 – 30, 2025 Calgary, Alberta".

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Some International initiatives to face current and future challenges:

- HTAi Rare diseases Interest Group
- IHI RealiseD Project

Why do we need a New Paradigm for Evidence Generation and Assessment in Rare Disease Technologies



- Inherent characteristics of Rare Diseases **not well understood outside** the rare community (nor its impact in **evidence generation**)
- Differences in regulatory and HTA approaches on **evidence expectations and interpretation** between major agencies
- RWE, surrogate endpoints, biomarkers and digital outcomes **not yet well accepted as good evidence**
- **Evidence for Rare ALWAYS graded** in current evidence assessment frameworks (EAF) as **low evidence and high uncertainty**

Consequences:

Health inequalities:

Increasing disparity in medicines available to treat RD between different countries and within countries

Source: QVIA, Global Trends in R&D 2024, Feb 2024)

HTAi WEBINAR

Why do we need a New Paradigm for Evidence Generation and Assessment in Rare Disease Technologies?

Thursday FEBRUARY 27, 2025 | 02.00 - 3.30 PM GMT+1



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compRehensive mEthodological and operational Approach to
cLinical trIals in ultra-rarE Diseases



IHI RealiseD

Kick Off Meeting 2025
Vienna, January 2025



This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101165912. The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, Europa Bio, MedTech Europe, and Vaccines Europe. Views and opinions expressed are those of the author(s) only. They do not necessarily reflect those of the Innovative Health Initiative Joint Undertaking and its members, who cannot be held responsible for them.

Aim & Scope of the topic

The aim of RealiseD is to change the paradigm for clinical trials in ultra-rare diseases. By bringing together all stakeholders, including clinicians, methodologists, pharmaceutical industry, patients, regulators and HTA body,

RealiseD will catalyze the development and acceptance of innovative approaches for evidence generation , analysis and data interpretation

Focus on paediatric and adult rare diseases. A 5 years project

Deliver methodological solutions for innovative clinical trial designs and analyses, including regulatory and HTA considerations (basket trials, platform trials, in silico trials, RWD, Digital Health Technologies, quantitative and qualitative approaches, trial with remote elements ...)

Identify good practices to address knowledge gaps including collection of natural history data, development of relevant new endpoints and of patient reported outcomes (PROs)

Scientific evaluation of regulatory and HTA assessment approaches, **using the concept of totality of evidence** in (U)RD.

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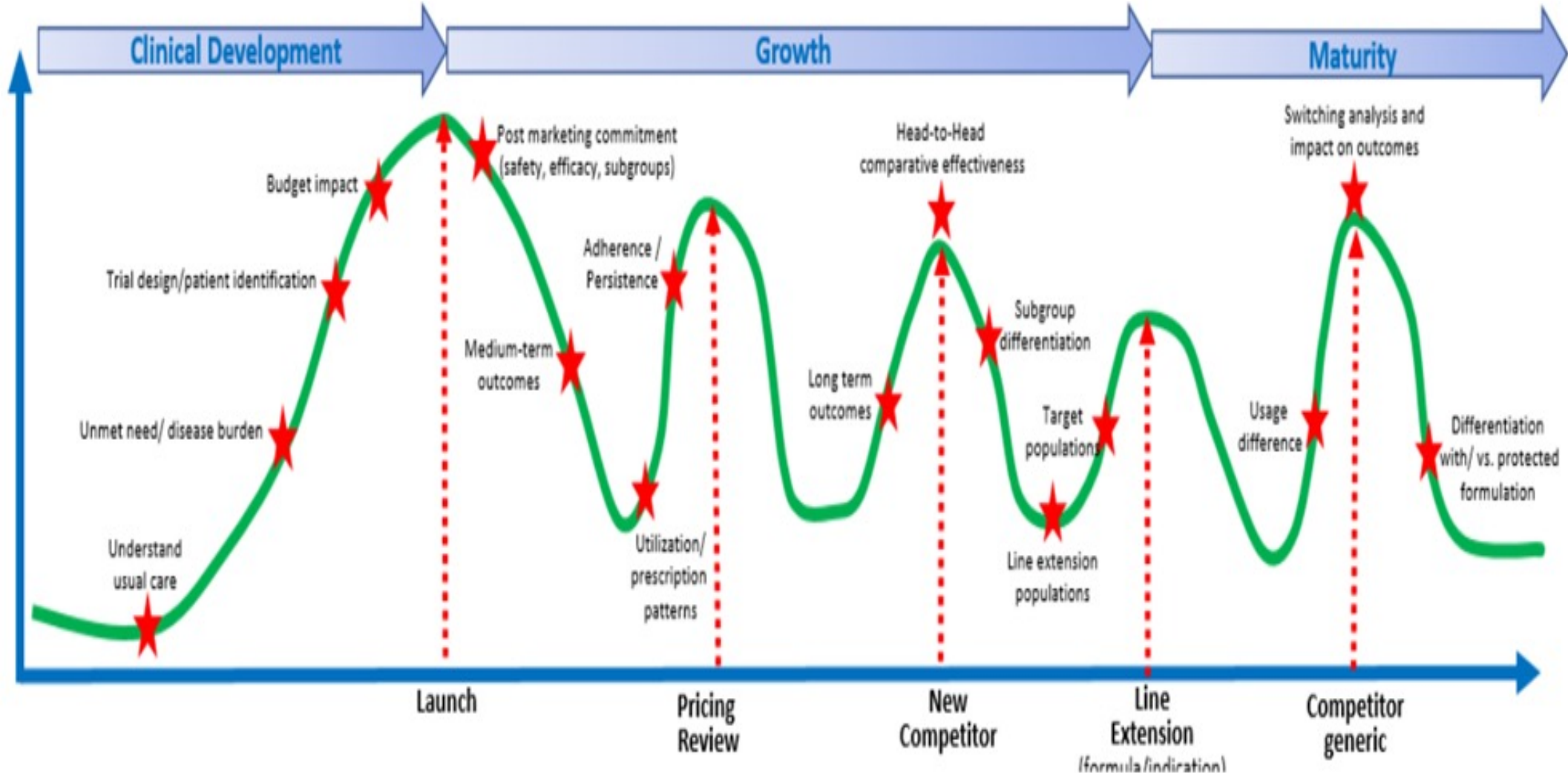
Final reflections

- **Global multi-stakeholder and multi-disciplinary collaboration** is crucial for **better data and evidence generation** but still is even crucial changing current paradigms in evidence assessment frameworks and its use for decision making.
- **Changing the paradigm** of the way rare evidence is assessed, not because we advocate for higher “flexibility” (meaning asking to reduce the quality of the scientific standards) but to **use more appropriately the scientific methods (design and analysis)** to help rare diseases.
- Advocating for a new global evidence assessment framework and the **acceptability of the concept “Totality of Evidence for Rare” including qualitative evidence from patients**



BACK UP SLIDES

Use of RWE during technology life cycle





Clinical

Demographics, EHR Data, Lab Test Results, Diagnoses, Procedures, Pathology/ Histology Data, Radiology Images, Microbiology Data, Provider Notes, Admission/ Discharge and Progress Reports, Performance Status



Medication

Medication Orders, Administration (Dose, Route, NDC/RxNorm codes), Concomitant Therapies, Point of Sale Data, (Prescription & OTC) Prescription Refill, Allergies



Claims

Medical Claims, Prescription Drug Claims, Other Drug and Treatment Use Data



Molecular Profiling

Genomic and Genetic Testing Data (SNPs/Panels), Multi-Omics Data (Proteomics, Transcriptomics, Metabonomics, Lipidomics), Other Biomarker Status



Family History

Historical Data on Health Conditions and Allergies Relating to Patient and Extended Family, Smoking Status, Alcohol Use



Mobile Health

Fitness Trackers, Wearable Devices, Other Health Apps Measuring Activity and Body Function



Environmental

Climate Factors, Pollutants, Infections, Lifestyle Factors (diets, stress), Other Environmental and Occupational Sources



Patient Reported

Patient Reported Outcomes, Surveys, Diaries (diets, habits), Personal Health Records, Adverse Event Reporting, Quality of Life Measures



Social Media

Patient Communities, Twitter, Facebook, Blogs



Literature

Disease Burden, Clinical Characteristics, Prevalence/Incidence, Rates of Treatment, Resource Use and Costs, Disease Control, Quality of Life Measures