Real World Evidence and Rare Disease Considerations across Regulatory and Health Technology Assessment Frameworks in the US, UK, and Canada

Lucas T.A. Blackmore, MPH, Kristen A. Cribbs, PhD, MPH, Betsy J. Lahue, MPH
Alkemi LLC, Manchester Center, VT, USA

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Background

- Provisions of the 2016 United States (US) 21st Century Cures Act include use of real-world evidence (RWE) to accelerate access to therapies in areas of high unmet need, such as rare disease
- The objective of this review was to evaluate published RWE frameworks to assess common topics, including rare disease considerations, across regulatory and health technology assessment (HTA) agencies

Methods

- HTA and regulatory agency websites in the US, United Kingdom (UK), and Canada were searched to identify real-world data (RWD) and RWE frameworks using pre-specified keywords (RWE, RWD, Framework, Guidance, Rare Disease, External Control) **(Table 1)**
- Inclusion criteria included: final framework version, English-language, and published between January 1, 2018, and December 31, 2023
- Four criteria were evaluated and scored for each identified framework using a binary scale (1=included), with a total possible score of 4 per framework (**Figure 1**)
- Descriptive analyses were conducted to assess framework comprehensiveness by country and agency type

Table 1. Targeted Agencies

	United States	United Kingdom	Canada
HTA	ICER Institute for Clinical and Economic Review	NICE National Institute for Health and Care Excellence	cadth Canada's Drug and Health Technology Agency
Regulatory	FDA U.S. Food & Drug Administration	MHRA Regulating Medicines and Medical Devices	Health Canada / Santé Canada

Figure 1. Framework Evaluation Criteria

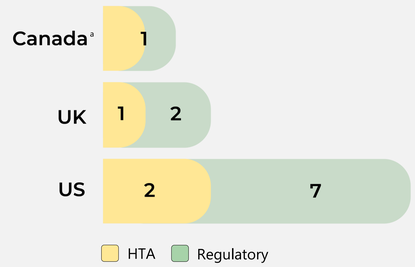
Which of these criterion were included in the RWE framework?

- Definition of RWE
- Data Specification/ Fit-For-Use
- Analysis Techniques/ Study Designs
- Special Consideration for Rare Disease

Results

- The review identified 13 endorsed frameworks[1-13] by 14 agencies **(Table 2)**, most of which were published by regulatory agencies (69%)[5-13] and agencies in the US (69%)[2,3,7-13] **(Figure 2)**
- Two frameworks, 1 HTA and 1 regulatory,[1,13] addressed all 4 criteria; One framework, published by a regulatory agency, did not address any criteria[5] **(Table 2)**
- 'RWE Definition' was the most covered criterion across frameworks reviewed **(Figure 3)**, with details presented in 11 frameworks,[1-4,7-13] while 'Special Consideration for Rare Disease' was covered in the least number of frameworks (n=3)[1,2,13]
- HTA frameworks covered a greater number of criteria, on average, than regulatory frameworks **(Table 2)**

Figure 2. Frameworks Reviewed (n=13)



[a]Two Canadian agencies (CADTH, HC) published a joint report

Figure 3. Summary of Framework Criteria Coverage

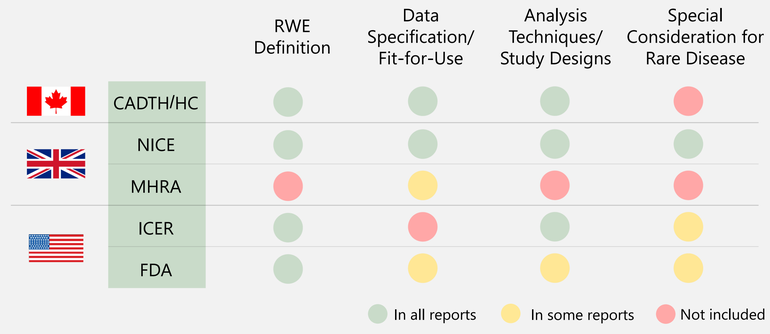


Table 2. HTA and Regulatory Frameworks (n=13)

	Frameworks Identified	Agency	Year	Criteria Met
HTA	1. NICE RWE Framework	NICE	2022	**4/4**
	2. Value Assessment Framework	ICER	2023	3/4
	3. Framework to Guide the Optimal Development and Use of RWE for Coverage and Formulary Decisions	ICER	2018	2/4
	4. Guidance for Reporting RWE[a]	CADTH/HC	2023	3/4
Regulatory	5. Guidance on the use of RWD in clinical studies to support regulatory decisions	MHRA	2021	**0/4**
	6. Guideline on RCTs using RWD to support regulatory decisions	MHRA	2021	1/4
	7. RWD: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products	FDA	2021	2/4
	8. Data Standards for Product Submissions Containing RWD Guidance for Industry	FDA	2023	3/4
	9. RWD: Assessing Registries to Support Regulatory Decision-Making	FDA	2023	2/4
	10. Considerations for the use of RWD and RWE to Support Decision-Making for Drug and Biological Products	FDA	2023	3/4
	11. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products	FDA	2023	3/4
	12. Submitting Documents Using RWD and RWE to FDA	FDA	2022	2/4
	13. Real-World Evidence Program	FDA	2018	**4/4**

[a]Joint report by CADTH and HC

Conclusions

- Few RWE frameworks included rare disease considerations
- US agencies published the majority of RWE frameworks identified
- While regulatory agencies published more frameworks, HTA agencies covered RWE topics more comprehensively

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Abbreviations: US, United States; RWE, real-world evidence; HTA, health technology assessment; UK, United Kingdom; RWD, real-world data; CADTH, Canadian Agency for Drugs and Technologies in Health; HC, Health Canada; NICE, National Institute for Health and Care Excellence; MHRA, Medicines and Healthcare products Regulatory Agency; FDA, United States Food and Drug Administration; ICER, Institute for Clinical and Economic Review; RCT, randomized controlled trial

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www.alkemihealth.com