Real-World Evidence (RWE) in Health Technology Assessment (HTA): Global Guidelines on the Use of RWE in Evidence Generation for HTA Evaluation

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INTRODUCTION

- Real-world evidence (RWE) studies utilize real-world data (RWD) to generate evidence about the usage, benefits, and risks of a medical product in routine clinical practice.[1]
- Heath technology assessment (HTA) bodies conduct systematic evaluations of medical products to inform healthcare decision-making.[2]
- Previous reviews of HTA submissions have identified an increased use of RWE, growing 33% from 2011 to 2021.[3] With the increasing utilization of RWE, HTA bodies are recognizing its importance in the evaluation of new technologies for reimbursement.
- However, there are several challenges in integrating RWE into the HTA process, including the ambiguity of HTA guidelines.

OBJECTIVE

- The objective of this study was to review global HTA guidelines on the use of RWE from different HTA archetypes to gain insights on the global RWE perspective.
- Official RWE requirements for each HTA body and the differences between the guidance were investigated to assist RWE researchers when conducting studies.

METHODS

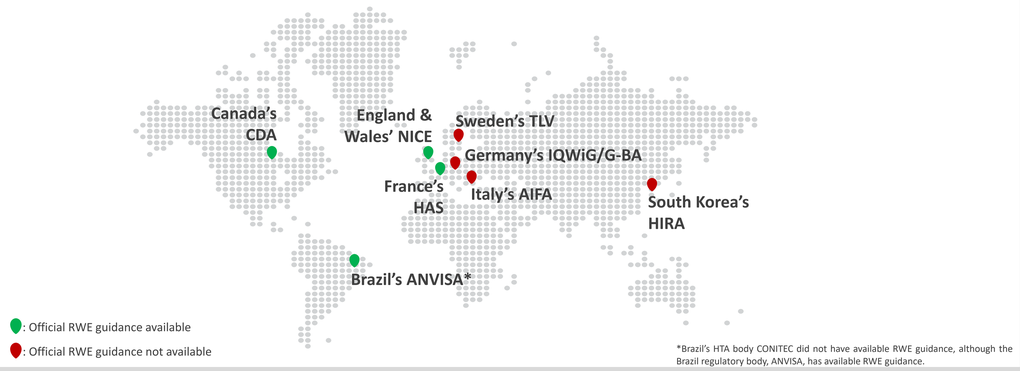
- To capture the global perspective of RWE, HTA bodies in eight countries were selected: Haute Autorité de santé (HAS) for France, National Institute for Health and Care Excellence (NICE) for England and Wales, Agenzia Italiana del Farmaco (AIFA) for Italy, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) / Gemeinsamer Bundesausschuss (G-BA) for Germany, Tandvårds- och läkemedelsförmånsverket (TLV) for Sweden, Canada's Drug Agency (CDA) for Canada [previously known as the Canadian Agency for Drugs and Technologies in Health (CADTH)], Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (CONITEC) for Brazil, and the Health Insurance Review and Assessment Service (HIRA) for South Korea.
- RWE guidance for eight HTA bodies was thoroughly investigated to determine which had published official guidance. Brazil's CONITEC did not have RWE guidance, although its regulatory body, Agência Nacional de Vigilância Sanitária (ANVISA), did. This was considered during this study to provide a global approach to RWE guidelines.
- Guidance documents were collected and documents which were not in English were translated using Google Translate. Data on the opinion and recommendations for RWE in evidence generation for technology appraisals was extracted and summarized.

TABLE 1. SUMMARY OF RWE GUIDANCE

Category	NICE[4]	HAS[5]	CDA[6]	ANVISA[7]
Study Design	Non-randomized studies, including traditional observational studies and clinical trials in which RWD can be used as an external control	Descriptive observational studies, comparative (including before-and-after or causal inference studies) or non-comparative depending on research question	Traditional observational studies (e.g., cohort studies) as well as pragmatic trials, causal inference methods	Observational studies, single-arm external control studies, pragmatic trials, and sequential clinical trials
Statistical Methods	Approaches to adjust for observed confounders: stratification, matching, multivariable regression and propensity score methods, or combinations; simple adjustment methods: stratification, restriction, and exact matching	Consideration of confounding factors include multivariate model with matching and/or adjustment for confounding factors or for high-dimensional or simple propensity scores, regression discontinuity designs, as well as other methods	Guidance does not recommend certain statistical methods; instead, it focuses on important reporting principles for methods used	Doubly robust estimates for propensity score methods, difference methods double, regression discontinuity designs, and sensitivity analyses to validate data quality and study results
Data Quality	Details of data quality including target concept, operational definition, quality dimension, how assessed, and assessment result should be provided for key study variables	Recommendations to produce good-quality data include maintaining documentation, minimizing patients lost to follow-up and missing data through adequate data monitoring and quality control, as well as others	Characteristics of data quality must be reported, including data completeness, validity of any data-cleaning algorithm(s), data extraction, and transformation processes	To improve data quality, transparency, and acceptability it is recommended to register the study protocol, have an appropriate strategy for controlling confounders, prioritize prospective and comparative study designs, and more
Outcomes	Primary and secondary outcomes should be defined and can include both patient and health system outcomes (such as resource use or costs)	Patient reported outcome measures (PROMs) should be integrated in the study and outcome measures are encouraged to be collected directly by patients	Detailed information on study outcomes and their definitions should be reported including the validity and relevance, considerations of misclassification, and the accuracy of timing in relation to exposure to the treatment(s)	Outcomes should be described and effect measures (e.g., risk ratio) should be presented in tables with any relevant comments
Challenges	Uncertainty in non-randomized studies will not typically be fully captured by the statistical uncertainty in the estimated intervention effect which represents a challenge in RWE studies	Methodological challenges exist due to the quality and scientific validity of real-world studies	Some challenges to consider include limitations of the data, sample size, generalizability, and clinical significance of results, in addition to typical discussions of bias and confounding	Challenges of RWE studies are related to the development and credibility of the results, and the evidence can be seen as weak; additional challenges are reported

Guidelines were summarized and detailed information should be viewed in the guideline/framework documents developed by each HTA/regulatory body.

FIGURE 1. RWE GUIDANCE AVAILABILITY



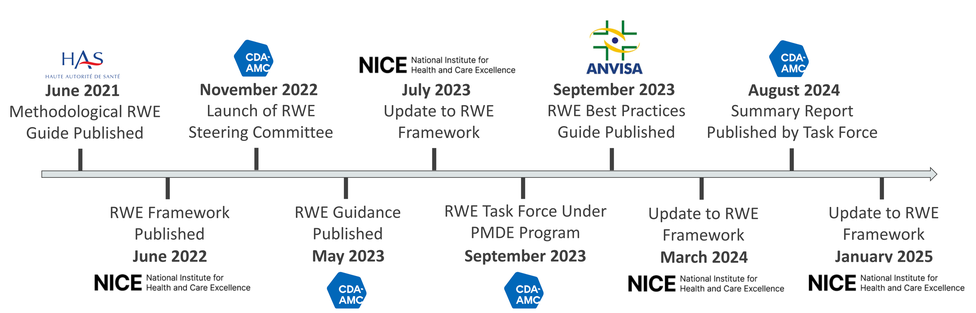
*Brazil's HTA body CONITEC did not have available RWE guidance, although the Brazil regulatory body, ANVISA, has available RWE guidance.

FIGURE 2. CONSOLIDATED REQUIREMENTS OF AN RWE STUDY SUBMISSION

- ☑ **Study Design and Research Questions**
- ☑ **Study Protocol and Summary**
- ☑ **Data Specifications, Sources, Delivery, Variables**
- ☑ **Participants**
- ☑ **Justification and Background**
- ☑ **Exposure Definitions and Comparators**
- ☑ **Statistical Methods**
- ☑ **Method Limitations**
- ☑ **Bias, Confounding, Effect Modifiers or Subgroup Effects**
- ☑ **Use of Outcomes and PROMs, Benefits and Risks**
- ☑ **Study Findings**
- ☑ **Interpretations and Generalizability**
- ☑ **Research Team Experience with Real-World Studies**
- ☑ **Final Considerations**
- ☑ **References**
- ☑ **Annexes and appendices**

[a]Brazil's ANVISA also requires reporting changes and updates, adverse events, and research team experience with real-world studies; UK's NICE requires reporting quality assurance standards and protocols, and patient attrition and characteristics.
[b]Detailed requirements for each country should be investigated in official guideline/framework documents.
[c]References 4-7

FIGURE 3. TIMELINE OF KEY ACHIEVEMENTS IN RWE GUIDELINES



[a]PMDE: Post-Market Drug Evaluation
[b]References 4-9

RESULTS AND DISCUSSION

- Out of the eight selected countries, four presented with RWE guidelines at the time of review including England and Wales, Canada, France, and Brazil (**Figure 1**).
- During the investigation, Italy, Germany, Sweden, and South Korea appear to accept RWE studies although no official guidance or framework was published during the time of this review. Italy's AIFA, for example, utilizes registry studies to track and manage the use of innovative drugs across the country.[10]
- RWE guidelines for each country vary in terms of what is most valued (**Table 1**). Similarities between the HTA/regulatory bodies exist including propensity score as a statistical methodology, defining study outcomes, emphasis on data quality, and overall challenges that exist with RWE studies.
- Several components are required for submission of RWE studies including a study protocol and summary, data specification, description of statistical methods, interpretation and generalizability, as well as others, which remain similar across NICE, HAS, CDA, and ANVISA (**Figure 2**).
- HAS was the first HTA body to publish RWE guidance in 2021, followed by NICE, CDA, then ANVISA (**Figure 3**). Since initial publication in 2022, NICE has updated its framework. Moreover, CDA has continued to advance its recommendations with a dedicated RWE task force in 2024.
- Similarly to ANVISA, other regulatory bodies have RWE guidance which should be investigated, like the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom.[11]
- In February 2025, the Institute for Clinical and Economic Review (ICER), an HTA body in the United States, supported the development of the Health Economics Methods Advisory (HEMA), which assembles NICE, CDA, as well as ICER, to evaluate new methods and processes for HTA review as a working group. Detailed RWE guidelines and best practices may be released by HEMA in the future, which may impact the broader HTA community.[12]

LIMITATIONS

- The ANVISA RWE guidance document was translated using Google Translate, and translation errors may therefore exisit. English guidelines for HAS were utilized which may also present with limitations.
- The number of HTA bodies was limited to eight, although other HTA bodies and regulatory bodies have published RWE guidance documents.
- Some countries may also have additional HTA bodies which are not reported, although they are not the main governing HTA body. For example, the HTA body named Institut national d'excellence en santé et en services sociaux (INESSS) in Québec is a provincial HTA body in Canada aside from CDA.

CONCLUSIONS

- The integration of RWE into HTA evaluation represents a significant evolution in how healthcare technologies are evaluated. While progress has been made globally to establish guidelines and frameworks for using RWE, ongoing efforts are needed to address existing challenges related to data quality, regulatory acceptance, and stakeholder engagement.
- RWE guidance is expected to continue to evolve with additional HTA bodies and regulatory bodies releasing guidance, and with advances in statistical methodology emphasizing artificial intelligence (AI) and machine learning (ML).
- Enhanced collaboration among industry players and regulatory bodies will be crucial in optimizing the use of RWE to support informed decision-making in healthcare.

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DISCLOSURES

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