ADVANCING HEALTHCARE DECISION-MAKING:

REAL-WORLD EVIDENCE AND ITS ROLE IN REGULATORY AND HEALTH TECHNOLOGY ASSESSMENT SUBMISSIONS

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Introduction

Real-World Evidence (RWE) is the evidence derived from real-world data (RWD) sources such as electronic health records, registries, insurance claims, personal tracking devices and clinical reported outcome measures. In recent years, RWE has become an essential **complement** to traditional randomized controlled trials (RCTs) in informing healthcare decision-making. As regulatory bodies and health technology assessment (HTA) agencies increasingly aim to expedite access to effective and cost-effective therapies, RWE can provide critical insights into the performance of medical interventions under routine clinical conditions. Unlike RCTs, which operate in controlled environments with narrowly defined populations, RWE captures the heterogeneity of real-world settings, thus potentially enhancing the external validity and generalizability of findings. These advantages, however, are tempered by important challenges, like being prone to different types of biases and confounding factors, that may limit their use.

In this article, we will explore the key characteristics of RWE studies and examine their growing acceptance by regulatory agencies and HTA bodies, highlighting recent trends in their use and providing perspective on future directions.

Main characteristics of RWE

RWE studies are primarily observational in nature, as they analyze data collected from real-world clinical practice without assigning interventions through randomization. These studies often utilize retrospective and prospective cohort designs, drawing on data from patient registries, electronic health records, and insurance claims databases. Unlike RCTs, which rely on strict inclusion criteria that may exclude patients with comorbidities or complex clinical profiles, RWE reflects the **heterogeneity of real-world populations.** This inclusivity allows for the assessment of treatment adherence, persistence, and sequencing, which are critical components of care delivery that RCTs often overlook. Consequently, clinical guidelines developed solely from RCT data may lack applicability to broader patient populations. RWE serves as a complementary approach, helping to bridge this gap and inform more inclusive and pragmatic evidence-based recommendations.[1]

RWE studies are characterized by **broad inclusion** and minimal exclusion criteria, which allow them to capture a diverse and representative patient population, including groups typically underrepresented or excluded from RCTs, such as older adults, children, pregnant women, and individuals with multiple comorbidities. This inclusiveness enhances the representativeness of findings and supports the development of guidelines that better reflect the realities of clinical practice across diverse patient demographics and geographic settings.

Another key strength of RWE lies in its ability to leverage large datasets, resulting in **substantial sample sizes**. This capability enables the evaluation of subpopulations and the detection of rare or infrequent outcomes that may be undetectable in smaller RCTs. Additionally, RWE studies often feature **longer and more variable follow-up periods**, aligning with the natural progression of clinical care. This extended observation period facilitates the evaluation of long-term safety and effectiveness, including the identification of rare or delayed adverse events that may not emerge during the relatively short timelines of phase III or IV trials.

The generalizability of RWE findings is enhanced by their reflection of routine clinical practice, thereby improving the **external validity** of study outcomes. Moreover, RWE offers flexibility in study design, enabling the investigation of research questions that are impractical or unethical to address through RCTs, such as studies involving rare diseases, high-risk populations, or system-level interventions. In scenarios where RCTs are infeasible, single-arm trials supplemented with real-world data as external comparators may provide a viable alternative to assess therapeutic effectiveness.

However, the observational nature of RWE introduces several **methodological challenges**. The absence of randomization means that treatment assignment is not controlled by researchers, rendering RWE studies susceptible to various sources of bias, including confounding, information bias, selection bias, and immortal time bias. These limitations necessitate the use of robust analytical methods to mitigate bias and enhance the credibility of findings derived from RWE. Despite these challenges, when appropriately designed and analyzed, RWE remains a valuable tool in complementing traditional clinical trial data and supporting decision-making in real-world healthcare contexts. **Table 1** summarizes the main differences between RWE studies and RCTs.

Table 1: RWE vs. Randomized Clinical Trials

Characteristic	RWE Studies	Randomized Controlled Trials
Study Design	Observational (non-randomized)	Experimental (randomized, often blinded)
Inclusion Criteria	Broad, inclusive, minimal exclusions	Strict, narrow, highly selective
Population	Heterogenous, reflects real-world diversity	Homogenous, selected for protocol adherence
Follow-up	Longer, variable, mirrors actual clinical practice	Fixed, protocol-driven, often shorter
Sample Size	Large, often population-level	Smaller, limited by resources and strict criteria
Treatment Patterns	Variable, reflects routine care and physician choice	Fixed, per protocol, standardized interventions
Data Sources	Electronic Health Records, claims, registries, patient-reported outcomes	Purpose-collected, trial-specific data
Outcomes	Broad, includes long-term and patient-centered outcomes	Predefined, focused on efficacy and safety endpoints
Setting	Real-world clinical environments	Specialized, controlled research settings
Patient Monitoring	Variable, as in routine care	Intensive, continuous, per protocol
Comparator	Often multiple, reflects real-world alternatives	Placebo or selected active comparator
Bias Risk	Higher (confounding, selection bias, lack of randomization)	Lower (randomization, blinding minimize bias)
Generalizability	High (applies to broader patient populations); external validity	Lower (results may not apply outside trial population); internal validity
Flexibility	Can address diverse questions and populations	Limited to protocol-specified questions and groups

Integration of RWE in Regulatory Submissions

Regulatory agencies such as the **U.S. Food and Drug Administration** (FDA) and the **European Medicines Agency** (EMA) increasingly recognize the value of RWE. In the U.S., the 21st Century Cures Act and subsequent FDA guidance have promoted the use of RWE for regulatory decisions, including label expansions, post-market surveillance, and rare disease indications.[2] The FDA's Advancing RWE Program, launched under the seventh reauthorization of the Prescription Drug User Fee Act (PDUFA VII) aims to improve the quality and acceptability of RWE in support of regulatory submissions.[2]

Similarly the EMA supports RWE in post-authorization safety studies (PASS), post-authorization efficacy studies (PAES), and within adaptive regulatory frameworks.[3] The EMA has documented and encouraged the use of RWE, especially through patient registries and its Data Analysis and Real World Interrogation Network (DARWIN EU®).[4]

Recent analyses evaluating FDA and EMA submissions across multiple therapeutic areas, including oncology, rare diseases, and neurology between 2009 and 2023, reveal a notable rise in RWE inclusion, particularly from 2019 onward.[5] RWE has been accepted in specific limited cases, predominantly in rare diseases and oncology. RWE was part of 189 novel drug applications and 45 label extensions. Additionally, 22% of submissions employed RWE for post-authorization evaluations of long-term safety and effectiveness.

Use of RWE in Health Technology Assessment (HTA)

In the United States, RWE is increasingly being integrated into reimbursement decision-making processes, particularly as the healthcare system transitions toward value-based care models. Organizations such as the Institute for Clinical and Economic Review (ICER) have pioneered the use of RWE to reassess therapies after market launch. ICER has piloted lifecycle-based HTA frameworks in which treatments are evaluated iteratively, incorporating RWE as it becomes available over time.[6] One illustrative case involved a 24-month RWE reassessment that demonstrated both the strengths and limitations of real-world data in refining clinical and economic evaluations. Beyond reassessment, RWE has also become foundational in supporting market entry agreements (MEAs), particularly value-based agreements (VBAs), which link reimbursement to treatment performance in real-world settings rather than relying solely on traditional volume- or price-based models. These agreements depend heavily on high-quality RWE to monitor outcomes, assess effectiveness, and guide ongoing reimbursement decisions.[7]

Use of RWE in Health Technology Assessment (HTA)

In **Europe**, the regulatory landscape is also evolving to incorporate RWE more systematically into HTA processes. The EU HTA Regulation (Regulation [EU] 2021/2282), which takes effect in January 2025, mandates joint clinical assessments across member states, initially focusing on oncology treatments and advanced therapy medicinal products (ATMPs).[8] This regulation explicitly promotes the use of RWE, particularly in scenarios where RCTs are limited or infeasible. The growing recognition of RWE's utility in HTA is reflected in a 2022 survey conducted by the European Network for Health Technology Assessment (EUnetHTA), in which 82% of respondents emphasized the importance of broader and more systematic integration of RWE. This support was particularly strong for the assessment of orphan drugs, diagnostics, and surgical interventions. Despite this progress, challenges remain. Some regional HTA bodies continue to exhibit reluctance in accepting RWE generated outside their own jurisdictions, underscoring the need for greater harmonization and trust in international data sources.[9]

Challenges in Utilizing RWE

Limitations for the use of RWE for regulatory and HTA submissions were identified in an SLR that was conducted by Evidinno.[10] One fundamental concern is the quality of source data. Administrative and claims databases, while large and often timely, frequently lack the clinical detail necessary for robust analysis. These data sources are also prone to issues such as disease misclassification, inaccurate or inconsistent coding, and missing information on important confounding variables.[11] Another common challenge is the formulation of poorly defined research questions. Clearly specified research objectives are essential, as they determine the feasibility and direction of the study. Misalignment between the research question and the needs of key stakeholders can compromise the relevance and impact of the resulting evidence.

Moreover, the observational nature of RWE research makes it inherently susceptible to various biases, including selection bias, immortal time bias, and confounding. Therefore, studies must clearly define critical elements such as the study objectives, target population, interventions, comparators, outcomes, and duration of follow-up.[12] Upholding scientific rigor requires the pre-specification of analytical strategies and the incorporation of multidisciplinary expertise in study design and protocol development.[13]

Finally, transparency and credibility are paramount in the interpretation and acceptance of RWE. Given the complexity of analyses and the potential for bias, it is essential to promote openness in methodological approaches. Public registration of study protocols, including detailed statistical analysis plans, strengthens the credibility of RWE studies and fosters greater confidence among regulatory bodies and other stakeholders.

Strategies for Optimizing RWE Integration

Enhancing the quality and accessibility of data is a cornerstone for generating reliable RWE. This begins with a thorough evaluation of data sources to ensure completeness, accuracy, and relevance to the research question. It is equally important to validate data against external benchmarks and address any inconsistencies, particularly when integrating multiple datasets from heterogeneous sources. Moreover, sustained investments in health information infrastructure, such as electronic health record (EHR) systems, data standardization protocols, and interoperability frameworks, are essential for building long-term capacity to support high-quality RWE generation.[14]

The application of strict and methodologically sound research practices is vital. Adhering to well-established pharmacoepidemiologic principles ensures the scientific integrity of RWE studies. These principles encompass careful study design, appropriate comparator selection, rigorous confounding adjustment, and the application of validated analytical techniques. Importantly, study protocols should be aligned with guidance provided by regulatory agencies and HTA bodies before the initiation of the research. Regulatory engagement at the protocol development stage allows for feedback on key design elements such as population definition, exposure measurement, outcome ascertainment, and analytic strategy, thus minimizing the risk of methodological flaws and misalignment with evidentiary standards.

Promoting transparency in research practices further strengthens the reliability and credibility of RWE. Public registration of study protocols, including detailed statistical analysis plans, allows for independent scrutiny and reduces the risk of selective reporting or post hoc modifications. Any amendments to the original protocol should be clearly documented and justified. Early alignment with the expectations of HTA bodies and regulatory authorities during study planning also facilitates the integration of RWE into policy and clinical decision-making. Best practice guidelines, such as those developed jointly by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE), provide essential frameworks for conducting high-quality secondary data analyses and real-world studies. These guidelines help standardize methodologies, enhance reproducibility, and promote stakeholder confidence in the evidence generated.[15]

Future Directions

1 Stakeholder Collaboration

Differing expectations between HTA agencies regarding the value and acceptability of RWE necessitates ongoing dialogue. Variability in evidentiary standards can lead to inconsistent evaluations and hinder the efficient use of RWE across jurisdictions. Efforts like the EU HTA Regulation aim to harmonize assessments and reduce duplicative evaluations.[16-18] Collaborative frameworks help ensure RWE meets the expectations of both regulators and payers. Regulatory bodies, HTA agencies, industry, payers, academia, and patients working together to align data standards, methodology, and evidentiary expectations.

2 The use of Artificial intelligence to enhance RWE

Artificial intelligence (AI) has shown the ability to identify hidden patterns in large datasets and detecting anomalies to reduce bias. These capabilities can improve data quality and analytical precision, ultimately supporting more reliable and nuanced insights. However, the use of AI must be transparent, reproducible, and interpretable to meet the evidentiary standards. As the use of AI in healthcare research continues to expand, formal guidance from regulatory and HTA agencies will be essential to standardize its application and establish clear expectations for methodological rigor and ethical use.

Conclusion

The integration of real-world evidence into regulatory and HTA frameworks represents a paradigm shift in the evaluation of health technologies. By complementing the rigor of RCTs with insights from routine clinical practice, RWE can enhance the relevance, inclusivity, and timeliness of evidence used in healthcare decision-making. However, challenges such as data quality, methodological rigor, and stakeholder alignment must be proactively addressed. As regulatory and HTA landscapes evolve, investing in transparent, high-quality, and collaborative approaches will be critical to realizing the full potential of the increased use of RWE to deliver meaningful patient-centered, cost-effective, and innovative healthcare solutions.

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