

# The Expanding Role of Real-World Evidence (RWE) in Supporting Regulatory Submissions

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## ABSTRACT

In an increasingly complex regulatory and therapeutic landscape, Real-World Evidence (RWE) is emerging as a resilient and innovative complement to traditional clinical trials, especially where randomized controlled trials (RCTs) are not feasible. Global Capability Centers (GCCs) are well-placed to scale RWE efforts using real-world data and support global regulatory decisions. Drawing from a review of 85 regulatory submissions, this presentation underscores how RWE has been utilized to:

- Bridge data gaps in rare diseases or ethical-constrained scenarios
- Accelerate approvals through regulatory designations such as FDA Fast Track and Orphan Drug pathways
- Support both original marketing applications (69%) and label expansions (31%), with oncology (36%) being the most represented therapeutic area

Regulatory acceptance of RWE is steadily increasing, with 72% of submissions leading to positive outcomes, despite a few facing challenges like methodological bias and data limitations. This reflects a growing yet cautious confidence among regulators, emphasizing the need for standardization, bias reduction, and transparent protocols. A key example in this context is the case of Blinatumomab (Blinicyto®), approved for a rare pediatric oncology indication where RWE was used as an external comparator in a single-arm trial. With a robust design that included propensity score matching and registry-based cohorts, the FDA granted accelerated approval – highlighting the regulatory potential of well-designed RWE approaches. However, the path to success is not without challenges. Key concerns include data heterogeneity and inconsistent coding standards, varying regulatory expectations across regions, and issues like selection bias and unmeasured confounding - each posing significant hurdles to the effective and consistent use of RWE in regulatory submissions. In conclusion, this presentation shows how the GCCs are not just adapting to a transforming regulatory world but actively paving the way with innovation, rigor, and real-world impact.

## INTRODUCTION

The landscape of drug development and regulatory science is undergoing a profound transformation as healthcare systems generate unprecedented volumes of patient-level information outside the confines of traditional clinical trials. Real-World Data (RWD) - derived from electronic health records, patient registries, medical claims, wearables, connected devices, and patient-generated health data - has emerged as a rich and diverse source of insights capable of complementing the evidence generated through randomized controlled trials (RCTs). While RCTs remain the gold standard for evaluating the safety and efficacy of medical products, their controlled environments and highly selective populations often limit generalizability to routine clinical practice. This gap has fueled a growing recognition of the need for evidence reflecting real-world patient experiences, treatment patterns, and outcomes across heterogeneous populations.

Real-World Evidence (RWE), defined as the clinical evidence derived from analysis and interpretation of RWD, is increasingly positioned as a critical component of modern regulatory decision-making. Regulatory agencies across the globe are embracing RWE to support various stages of the product lifecycle—from initial approvals and label expansions to post-marketing safety surveillance and effectiveness assessments. This shift is driven by the growing sophistication of data capture technologies, improved analytic methodologies, and the urgent public health need for faster, more efficient evidence generation.

The integration of RWE into regulatory submissions offers significant advantages: it enables the assessment of product performance in broader, more diverse populations; facilitates the study of rare diseases or conditions where RCTs are challenging; and accelerates evidence generation in time-sensitive scenarios such as pandemics or emerging therapeutics. Moreover, the iterative process of framing research questions, aggregating high-quality RWD, applying robust analytical techniques, and translating findings into actionable RWE insights aligns closely with the evolving expectations of regulatory bodies. As the industry continues to adopt innovative digital tools and data ecosystems, the role of RWE in regulatory science is expanding rapidly. This paper explores that evolution and highlighting current trends, regulatory expectations, methodological considerations, and the opportunities and challenges that define RWE's growing influence in shaping regulatory submissions.

## EVOLVING REGULATORY SUBMISSIONS

The regulatory landscape has progressively embraced Real-World Evidence (RWE) as a credible and complementary source of clinical insights, reflecting a broader shift toward data-driven, patient-centered decision-making. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are increasingly acknowledging the role of RWE in strengthening drug development programs and informing regulatory submissions. This evolution is evident in the growing number of marketing applications supported by RWE, whether for initial approvals, label expansions, or post-approval commitments. By leveraging diverse real-world data (RWD) streams - ranging from electronic health records and patient registries to claims databases and patient-generated health data - regulators are better equipped to understand product performance in actual clinical settings.

A major catalyst for this shift is the 21st Century Cures Act, enacted in 2016, which established a structured framework for evaluating the regulatory utility of RWE. The Act aims to accelerate therapeutic innovation by encouraging sponsors to responsibly integrate RWE into submissions, particularly for rare diseases, unmet medical needs, and scenarios where traditional randomized controlled trials (RCTs) are infeasible or insufficient. Since its implementation, the Act has paved the way for clearer regulatory expectations, guidance documents, and methodological standards that support the consistent and scientifically robust use of RWE in decision-making. As RWE is increasingly incorporated across clinical development stages - from preclinical hypotheses to post-marketing safety assessments - regulatory agencies continue to emphasize the importance of transparency, data quality, and methodological rigor. Key evaluative questions now guide the acceptability of RWE studies: Is the data source fit-for-purpose? Are the statistical methods appropriate and robust? Is the analytical approach clearly communicated? And importantly, are the results reproducible? These principles ensure that RWE contributions maintain scientific credibility while expanding the evidence ecosystem beyond controlled trials. As the integration of RWE becomes more systematic and sophisticated, it plays an ever-growing role in shaping regulatory submissions, accelerating access to innovative therapies, and ultimately improving patient care.

## REGULATORY EVIDENCE INTEGRATION

As regulatory agencies increasingly rely on Real-World Evidence (RWE) to inform decision-making, the integration of real-world data into regulatory submissions demands a methodological framework that is both rigorous and transparent. RWE studies intended to support regulatory decisions must therefore demonstrate adherence to core methodological principles that ensure the validity, credibility, and reproducibility of findings. These considerations span the full lifecycle of study development—from defining the data source and designing the study, to conducting analyses, assessing outcomes, and clearly communicating assumptions and limitations.

A foundational step in regulatory-grade RWE generation lies in selecting a **fit-for-purpose data source**. High-quality, patient-level data with sufficient completeness, consistency, and representativeness are essential for generating reliable evidence. Study design must also align with the research objective, whether retrospective, prospective, or hybrid, and ensure that the data environment supports robust analyses. Eligibility criteria must be defined with careful attention to prognosis factors, potential confounders, and appropriate matching strategies to approximate the balance typically achieved in randomized trials. A clearly articulated **protocol and statistical analysis plan** is central to regulatory acceptance. These plans should outline prospective decisions, bias-mitigation strategies, and statistical assumptions. As demonstrated in the example study, methods such as stabilized inverse probability of treatment weighting (sIPTW), propensity score matching (PSM), Kaplan–Meier survival analyses, and Cox proportional hazards models can strengthen causal inference when applied judiciously.

The conduct of the study further shapes the reliability of RWE. Variations in diagnostic criteria, treatment patterns, dosing regimens, laboratory measurements, and intercurrent events must be recognized and accounted for. Equally important is the assessment of outcomes, which must rely on objective, validated measures, standardized definitions, and transparent reporting. Safety assessments, identification of adverse events, and survival analyses illustrate how structured outcome evaluation enhances credibility.

By systematically applying these methodological considerations, RWE can be transformed into regulatory-ready evidence that meaningfully supports FDA decision-making. The worked example highlights how real-world clinical practice patterns and comparative safety insights can be rigorously analysed to complement traditional evidence and contribute to more informed regulatory evaluations.

## KEY RWE TRENDS IN 2025

In 2025, Real-World Evidence (RWE) is undergoing a significant transformation driven by regulatory, technological, and patient-centric advancements. Regulatory bodies are increasingly accepting de-identified RWE without the need for patient-level data, expanding access to valuable sources such as EHRs, registries, and claims databases. At the same time, advances in artificial intelligence and machine learning are enabling more sophisticated analyses, allowing researchers to identify complex patterns, predict outcomes, and support personalized treatment strategies.

Global collaboration is further strengthening the RWE ecosystem, with international partnerships establishing aligned standards that facilitate cross-border data exchange and enhance the comparability of evidence across healthcare systems. Importantly, patients are now active contributors to evidence generation through wearables, mobile health technologies, and registries, improving the real-world relevance, depth, and quality of collected data and reinforcing the role of RWE in informed healthcare decision-making.

## OUTCOMES

The expanding application of Real-World Evidence (RWE) has created substantial opportunities to enhance clinical understanding, regulatory decision-making, and health-care delivery. RWE is increasingly recognized for its ability to justify non-randomized trial designs, particularly external control arms, which are critical in situations where randomized controlled trials (RCTs) may be infeasible or unethical. By drawing on data from broader and more diverse patient populations, RWE strengthens the representativeness of clinical insights and supports regulators in evaluating trial feasibility, safety, and effectiveness in real-world settings. Additionally, RWE contributes meaningful context through natural history studies and provides external benchmarks that enrich the interpretation of single-arm trials—an area of growing importance across oncology and rare diseases.

Importantly, RWE helps address critical gaps that arise when certain patient groups remain underrepresented in traditional trials. Clinicians often lack evidence to guide treatment decisions for populations such as the elderly, racial and ethnic minorities, and socioeconomically disadvantaged individuals. Well-designed RWE has the potential to mitigate these disparities by generating insights that reflect everyday clinical practice and heterogeneous patient characteristics. This broader evidence base ultimately supports more informed and inclusive treatment strategies. Beyond its clinical relevance, RWE is increasingly viewed as a strategic investment within drug development. With costs generally accounting for less than 3% of the development budget, RWE offers a cost-effective means to inform early decision-making, enhance portfolio planning, and provide external validation for clinical programs. It also serves as a safeguard in trial execution, enabling agile adaptation to evolving regulatory expectations. By offering credible external benchmarks and accelerating development timelines—especially when used as an external control arm—RWE builds a compelling value narrative for both regulators and payers. Together, these outcomes underscore the expanding value of RWE as both a scientific and strategic asset across the product lifecycle.

## PAPER REVIEW

The paper “*Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases*” conducted a comprehensive landscape review to understand how Real-World Evidence (RWE) has been utilized to support regulatory submissions and assess the extent of its acceptance across global health authorities. By systematically evaluating 85 regulatory applications that incorporated RWE, the review provides clear evidence of its expanding role in regulatory science and its increasing credibility in decision-making.

The review aimed to:

- Assess how RWE has been applied within regulatory submissions across various therapeutic areas
- Identify trends in the types of RWE studies used, data sources leveraged, and regulatory outcomes influenced
- Highlight use cases demonstrating how RWE strengthened safety evaluations, effectiveness assessments, and label expansion requests

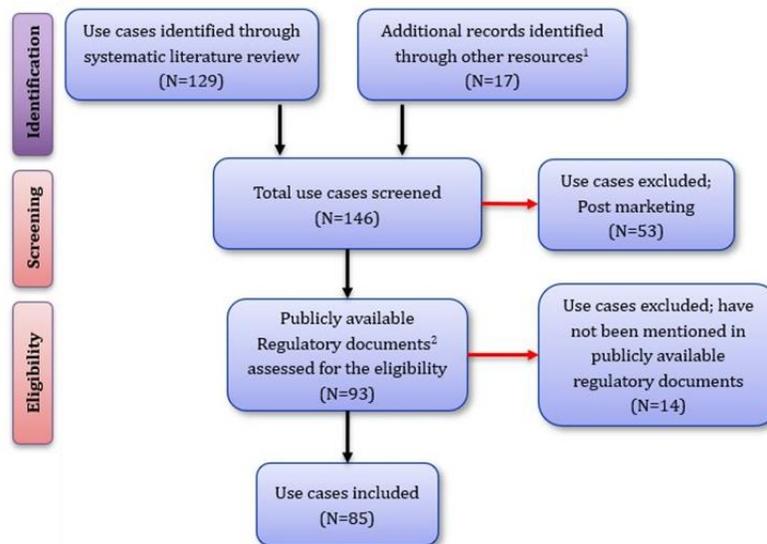
Insights from the review reinforce the growing emphasis by regulators - particularly the FDA and EMA - on integrating RWE into:

- Safety evaluations
- Effectiveness determinations
- Label expansion submissions
- Supportive evidence for non-randomized designs

This aligns with an ongoing shift toward incorporating real-world clinical practice data to complement or substitute traditional RCT evidence, especially in situations where RCTs are not feasible or ethical.

The paper's review pipeline comprised:

- 129 use cases identified through systematic literature review
- 17 additional cases identified from secondary sources
- 146 total cases screened
- 93 publicly available regulatory documents assessed for eligibility
- 85 final use cases included after exclusions (post-marketing cases and cases lacking regulatory documentation)



**Figure 1:** Pipeline for the selection of use cases

The key observations include:

- **85%** of included use cases relied on retrospective observational studies -highlighting the practical value of existing real-world datasets
- Therapeutic areas represented: **oncology, rare diseases, and chronic conditions**, where patient diversity and unmet needs often limit the feasibility of RCTs
- Studies commonly leveraged large real-world datasets to support comparative effectiveness, safety assessments, and contextual benchmarks

The paper provides strong evidence that:

- RWE meaningfully contributes to regulatory evaluations
- Well-designed RWE studies are increasingly accepted as supportive evidence
- Regulators value RWE's ability to reflect broader, more representative patient populations

## **CASE SPOTLIGHT: BLINATUMOMAB AND THE POWER OF RWE IN REGULATORY DECISION-MAKING**

The case of Blinatumomab (Blinicyto®) offers a compelling demonstration of how robust Real-World Evidence (RWE) can meaningfully support regulatory approvals, particularly in rare and high-unmet-need oncology indications. For select B-cell acute lymphoblastic leukemia (ALL) subtypes, conventional randomized controlled trials (RCTs) were challenged by feasibility and ethical constraints - making RWE an essential complement to clinical trial data.

Regulatory agencies including the FDA (2014, 2018) and EMA (2015) incorporated RWE to:

- Support the **original marketing application approval** using external real-world control cohorts
- Enable **label expansion** based on retrospective real-world clinical outcomes
- Strengthen evidence where traditional comparative trials were not practical due to rarity of populations

Primary endpoints assessed through RWE included:

- Complete Remission (CR/CRh)
- Hematologic relapse-free survival (HRFS)
- Overall survival (OS)
- Minimal residual disease (MRD) negativity

RWE showed clear clinical benefits versus historical controls:

- **CR rate:** 34% vs. 16% ( $p < 0.001$ )
- **Median OS:** 7.7 months vs. 4 months ( $p = 0.01$ )
- **MRD negativity:** 76% vs. 48%

These outcomes provided regulators with strong comparative insight, reinforcing the therapeutic value of Blinatumomab in a population where trial-based comparators were limited.

Key Learnings were:

- **Enabled access** for a rare paediatric population where evidence gaps existed.

- Demonstrated **regulatory-grade application** of synthetic control arms
- **Bridged feasibility gaps** where RCTs were impractical due to rarity and ethical concerns
- Highlighted how high-quality RWE can **accelerate approvals and expand indications**

## KEY CHALLENGES

As RWE is just an evolving space around the regulatory submission, there are some key challenges which it faces at this initial stage, which are:

- **Data heterogeneity:** Variability in coding standards, care settings, and geographies complicates data linkage, completeness, and comparability.
- **Methodological consistency:** Lack of uniform protocols for cohort definitions, endpoint ascertainment, and handling of missingness limits reproducibility.
- **Bias and confounding:** Selection bias, immortal-time bias, and unmeasured confounding remain core threats in non-randomized datasets.
- **Regulatory harmonization:** Differences in expectations across regions create uncertainty for global programs and cross-submission reuse.
- **Interoperability with trials:** Limited integration of RWE with RCT frameworks (e.g., hybrid designs, pragmatic extensions) reduces cumulative evidence strength.
- **Operational readiness:** Data governance, provenance tracing, and auditability are uneven across data partners.

## FUTURE VISION

The future of RWE lies in building globally aligned, analytically robust, and seamlessly integrated evidence frameworks that elevate its role across the entire drug development and regulatory lifecycle.

- **Global alignment on RWE standards:** Converge on common data models, transparency checklists, and fit-for-purpose frameworks to enable reusability.
- **Advanced analytics for causal inference:** Scalable use of AI/ML with rigorous diagnostics (e.g., balance metrics, negative controls, sensitivity analyses).
- **Expanded regulatory use cases:** Systematic adoption in label expansions, post-marketing safety/effectiveness, rare diseases, pediatrics, and external control arms.
- **Collaborative data ecosystems:** Federated networks and disease registries designed for regulatory-grade endpoints and longitudinal follow-up.
- **Embedded RWE pathways:** Bake RWE into development plans, with prospective protocols, SAPs, and submission-ready documentation.

## CONCLUSION

Real-World Evidence (RWE) has emerged as a critical and credible component of modern regulatory science, especially as health authorities increasingly seek evidence that reflects real-world patients, practices, and outcomes. Across this paper, we have demonstrated how RWE strengthens regulatory submissions by addressing feasibility gaps, enhancing safety and effectiveness evaluations, and enabling accelerated or expanded approvals - particularly in rare diseases and oncology. Through structured methodological frameworks, careful data curation, and transparent analytical approaches, RWE can reliably complement or, when necessary, substitute traditional clinical trials. Evidence from the landscape review and case studies, including Blinatumomab, reinforces how well-designed RWE can influence pivotal regulatory decisions. As regulatory expectations evolve, the future of RWE will depend on global standardization, advanced analytics, and seamless integration into lifecycle planning. Ultimately, RWE represents not just an alternative evidence source, but a transformative tool that expands access to therapies and supports more timely, equitable patient care.

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