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APAC 2026

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

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Agenda

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- **Evolving Regulatory Submissions**
- **Regulatory Evidence Integration**
- **Outcomes**
- **Key RWE Trends in 2025**
- **Paper Review:** Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases
- **Spotlight:** Blinatumomab (Blincyto®) Leveraging RWE for Regulatory Approval in a Rare Pediatric Cancer Regulatory Context
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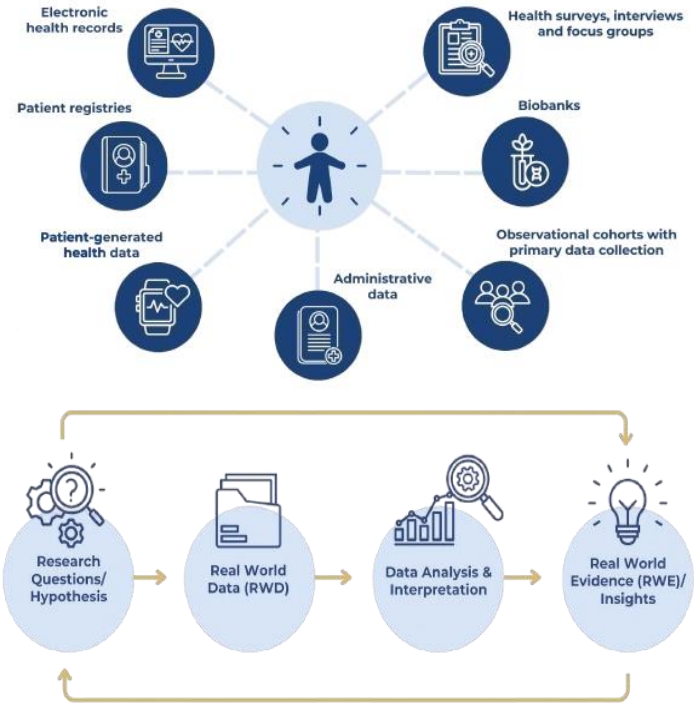
Real World Evidence

Real World Data (RWD) are the data relating to areas such as patient health status and/or the delivery of health care not collected in conventional randomized controlled trials (RCT), including sources such as electronic health records (EHRs), wearables, connected devices, medical claims data, and product, patient, and disease registries.

RCT REMAINS THE GOLD STANDARD IN ASSESSING A TREATMENT'S SAFETY AND EFFICACY

Real-world evidence (RWE) is the clinical evidence obtained from RWD, with regard to the use, potential benefits or potential risks associated with a medical product. It can be used to supplement RCT in terms of product efficiency and effectiveness.



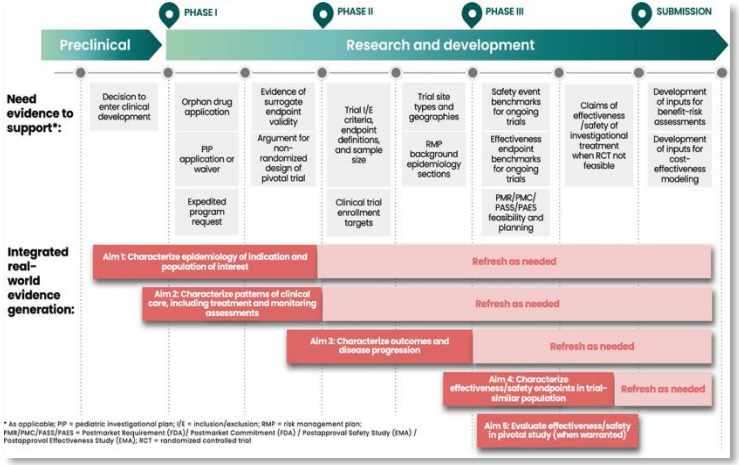
Evolving Regulatory Submissions

Growing Acceptance by Regulatory Agencies

Regulatory bodies like the FDA and EMA are increasingly incorporating Real-World Evidence (RWE) in drug approvals, support approval of new indications for already-approved drugs (Label expansions) and Support or fulfill post-approval study requirements.

21st Century Cures Act & RWE

The 21st Century Cures Act, signed into law in December 2016, has helped to create a framework to evaluate the use of Real-World Evidence (RWE) in regulatory decision-making for drugs and biological products, aiming to accelerate medical product development and patient access to innovations



Integrating RWE into clinical development

Key Questions for evaluating RWE studies

- What is the Quality of the data source?
- Were appropriate statistical methods applied?
- Is the analytical research approach transparently communicated?
- Is the study replicable or reproducible?

Regulatory Evidence Integration

Protocol and statistical analysis plan
- Prospective plan
- Bias mitigation
- Statistical analysis assumption

Data Source and Study Design
- Data quality and standard
- Patient-level data
- Fit for purpose

Study Conduct
- Diagnostic methods
- Available Treatments
- Dosing regimens
- Variations in clinical practices
- Health data recording
- Intercurrent events

Methodological Considerations

Eligibility Criteria
- Important prognosis factors
- Possible confounding
- Matching strategies

Outcome assessment
- Objective outcomes
- Potential bias
- Standard approaches
- Validity of the assessment tools

Application of RWE to support FDA regulatory decision making

Regulatory Evidence Integration

Protocol and statistical analysis plan
- Baseline and Clinical Characteristics
- Treatment patterns and sequence
- KM and COX models

Data Source and Study Design
- EHR Flatiron data
- Retrospective study
- sIPTW and PSM cohorts
- Safety assessment

Methodological Considerations

Study Conduct
- Drug class exposure
- IMiD vs PI vs AntiCD38
- Standard dosing regimens
- Clinical lab values
- Adverse events reporting

Eligibility Criteria
- Diagnosed with MM
- Received IMiD during the study period
- Exclude clinical trial participants

Outcome assessment
- Incidence assessment
- Identification of adverse events
- Survival analysis
- Treatment comparisons

Application of RWE to support FDA regulatory decision making

Key RWE Trends in 2025

Expanded Regulatory Acceptance
A historic FDA policy shift now accepts de-identified RWE in applications without requiring patient-level data. This unlocks access to sources like cancer registries, EHR networks, and insurance claims that were previously excluded from submissions

Advanced Analytics (AI & ML)
Artificial intelligence and machine learning are revolutionizing RWE by identifying complex patterns and predicting outcomes. These technologies enable precise personalization of treatment plans based on individual patient characteristics

Global RWE Collaboration
International partnerships are establishing unified RWE standards to facilitate cross-border data exchange. This global approach ensures findings are accessible, comparable, and applicable to healthcare systems worldwide.

Patient-Centric RWE
Patients are now active contributors to evidence generation through wearables, mobile health apps, and registries. This direct engagement significantly enhances the quality, depth, and real-world relevance of collected data

Outcomes

Accepted and Emerging Uses of RWE

- Justify non-randomized trial designs (e.g., external control arms)
- Demonstrate representativeness of trial populations
- Support regulatory discussion on trial feasibility
- Support natural history studies for disease context
- Provide external benchmarks to interpret single-arm trials
- Strengthen safety/effectiveness insights in trial-similar populations
- Optimize eligibility/patient selection criteria
- Bridge gaps were RCTs are not feasible

Appropriate and well-designed RWE has the potential to fill knowledge gaps by offering access to broader, more representative findings, which physician can use to inform treatment decisions for their patients.

Underrepresentation in clinical trials can leave clinicians without enough information to make treatment decisions for patients from underrepresented groups.

- Socioeconomically disadvantaged patients
- Racial and ethnic minorities
- The elderly

RWE as a Strategic Investment

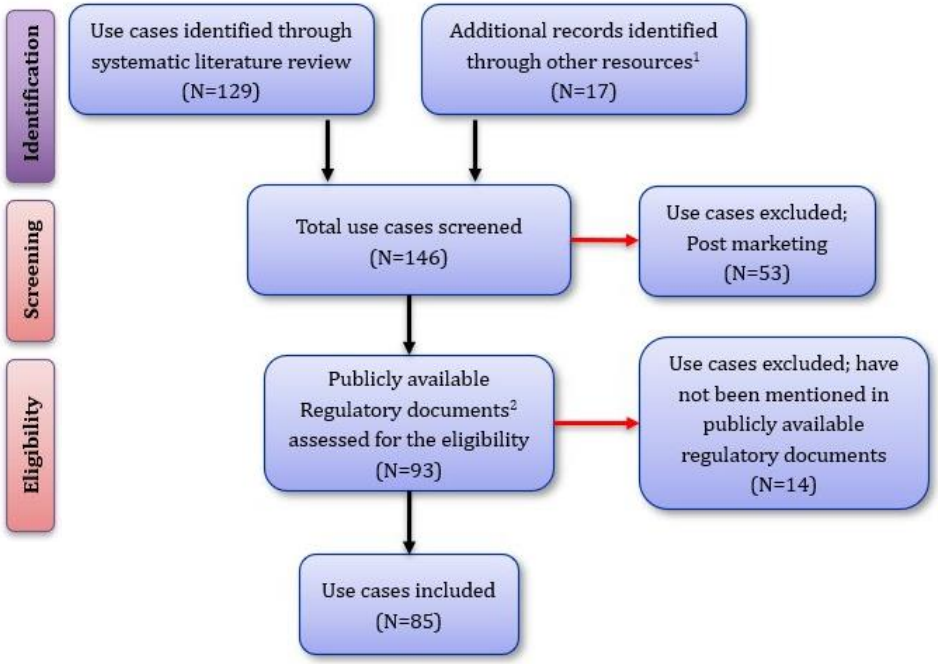
- RWE studies cost <3% of drug development budget
- Enables evidence-based decisions early in development
- Serves as a strategic safeguard in trials
- Provide external benchmarks to interpret single-arm trials
- Builds a strong value narrative for regulators and payers
- Improves portfolio planning
- Enables agile adaptation to evolving regulatory standards
- Accelerates timeline as an external control arm

Paper Review: Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases

📜Purpose of Paper
- Assess how real-world evidence (RWE) has been used to support regulatory submissions by reviewing 85 regulatory applications with RWE

⚖️Regulatory Context
- Growing emphasis by FDA and EMA on integrating RWE into regulatory decision-making
- Focus areas: safety evaluations, effectiveness determination, and label expansions

👥Cohorts Assessed:
- 85% of use cases were retrospective observational studies
- Case studies include various therapeutic areas (oncology, rare diseases, chronic conditions)



Reference paper

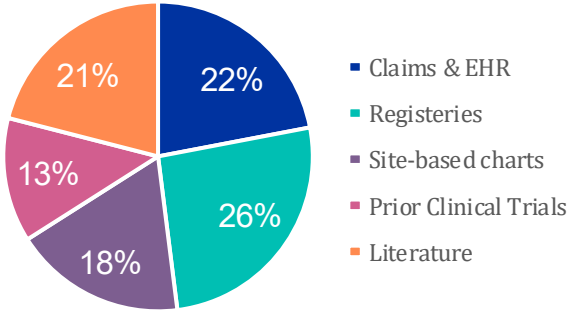
[1] ASCO
[2] FDA and EMA

Paper Review: Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases

Out of 85 use cases reviewed

- **36.5%** of RWE-based submissions were in **oncology**, underscoring its impact in accelerating cancer drug approvals
- 20% of submissions used **RWE as primary evidence**, bypassing traditional trials
- **69.4%** led to **original marketing approval**, followed by label expansion
- 49.4% used RWE to **support single-arm trials** (especially in rare diseases)
- **62.4%** were **retrospective RWD cohorts**
- Over **85%** of use cases captured RWE supporting **efficacy** or **both safety and effectiveness**

Sources of Data used



~85% of RWE-based use cases successfully supported regulatory submissions

Reference paper

Spotlight: Blinatumomab (Blincyto®) Leveraging RWE for Regulatory Approval in ALL Patients

🎯 RWE's Role in Accelerated Approval

Real-world evidence, in conjunction with clinical trial data, highlights Blinatumomab's role in addressing unmet needs for select B-cell ALL subtypes

Regulatory information	RWE study approach	Regulatory use type and purpose	RW primary endpoints
FDA (2014)/ EMA (2015)	External RWD controls (direct matching)/ Retrospective RWD Cohort	Original marketing application approval	CR + CR with partial hematologic recovery (CRh)
FDA (2018)		Label expansion	Hematologic relapse-free survival (HRFS)

Outcome Metric	Blinatumomab	Historical Results	P-value
Complete Remission (CR)[1]	**34%** (CI: 28.0–39.5)[2]	16% (CI: 10.0–23.0)[2]	<0.001
Median Overall Survival (OS)[1]	**7.7 months** (CI: 5.6-9.6)[3]	4 months (CI: 2.9-5.3)[3]	0.01
MRD Negativity[3]	**76%**	48%	-

💡Key Learnings:

- RWE enabled access for a rare pediatric population
- Demonstrated regulatory-grade use of synthetic control arm
- RWE bridged evidence gap where RCTs were infeasible due to rarity and ethical constraints

Reference paper

Conclusion

📌Real-World Evidence is increasingly recognized as a credible and complementary source of clinical insight, especially in areas where randomized trials are infeasible. By leveraging robust observational data, RWE helps bridge evidence gaps, inform regulatory decisions, and accelerate access to therapies - particularly in rare diseases, oncology, and precision medicine.

⚠️Key Challenges

- Data heterogeneity across sources and geographies
- Lack of methodological standardization in RWE generation
- Bias and confounding in non-randomized datasets
- Lack of global harmonization of regulatory expectations
- Limited inter-operability with traditional trial frameworks

🚀Future Vision

- Global Alignment on RWE Standards
- Advanced analytics (AI/ML) to improve data quality and causal inference
- Expanded use of RWE in label expansions, post-marketing surveillance, and rare disease approvals
- Collaborative registries to support external control arms
- Embedded RWE pathways in submission strategy and lifecycle planning

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