When Trials Fall Short: Leveraging Real-World Evidence to Advance Precision Therapies

PT40

Emily Nagel, PharmD Candidate[1]; Youssef M. Roman, PharmD, PhD[2]

1. University of Tennessee Health Science Center, College of Pharmacy
2. 2. Idaho State University, L.S. Skaggs College of Pharmacy

Background

RCTs remain the gold standard for establishing efficacy, yet they face limitations in advancing precision medicine:

- Small patient populations make traditional trials infeasible[1]
- Molecular heterogeneity requires subgroup-specific evidence
- Rare genetic disorders face high clinical need but low trial feasibility
- Strict inclusion and exclusion criteria
- Ethical concerns limit randomized placebo-controlled designs

Objectives

- Characterize RWE's evolving role in the regulatory life cycle of precision therapies[2]
- Assess RWE's capacity to address RCT limitations in rare diseases, oncology, and biomarker-driven indications
- Identify critical barriers to achieving regulatory-grade real-world data (RWD)

Methods

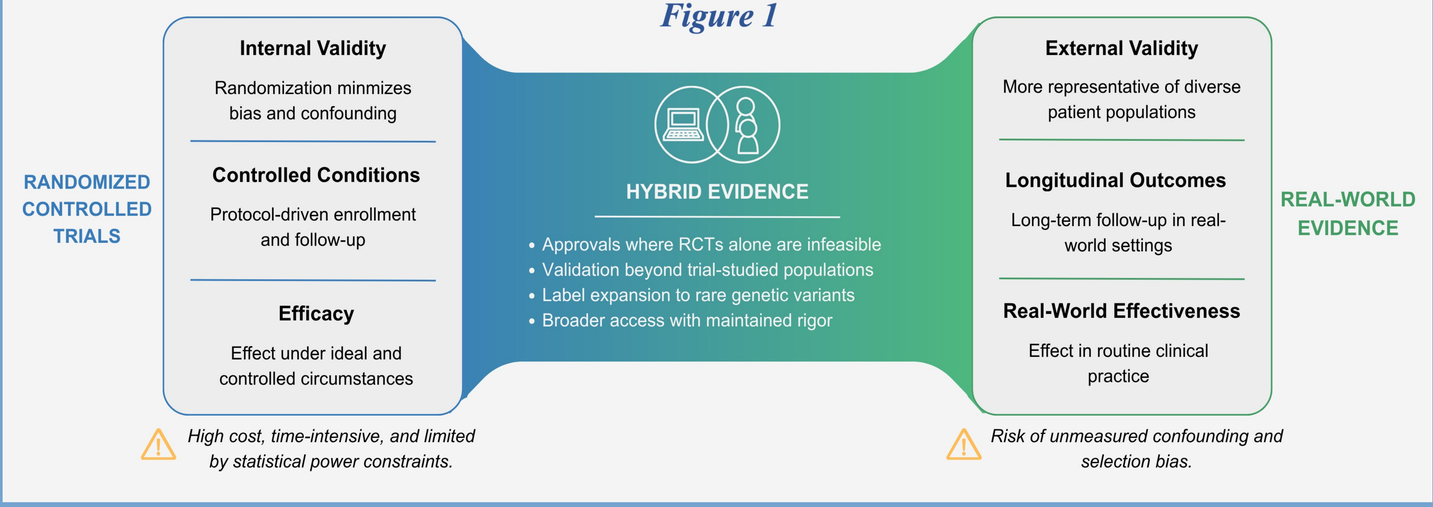
- Comprehensive review of FDA guidance documents and regulatory decisions utilizing RWE between January 2010 and December 2025.
- Analyzed integration of RWD (EHRs, claims databases, disease registries) in regulatory decision-making across the drug lifecycle.
- Assessed key applications: external controls for orphan drugs, biomarker-driven approvals, and post-market surveillance.

Abbreviations

- **RCT:** Randomized Controlled Trial
- **RWE:** Real-World Evidence
- **FDA:** U.S. Food & Drug Administration
- **EHR:** Electronic Health Record
- **MSI-H:** Microsatellite Instability-High
- **dMMR:** DNA mismatch repair deficiency
- **PD-1:** Programmed cell death protein 1
- **CFTR:** Cystic Fibrosis Transmembrane Conductance Regulator
- **CPS-1:** Carbamoyl phosphate synthetase 1

Complementary Evidence in Precision Medicine

Figure 1



RWE-Supported Regulatory Decisions

Table 1

Therapy (Class)	Indication(s)	Key Evidence Source	Regulatory Outcome
Pembrolizumab (Anti-PD-1 monoclonal antibody)	Unresectable or metastatic MSI-H or dMMR solid tumors	NGS database with claims-linked outcomes[3]	Validated efficacy in non-trial tumor types[4]
Ivacaftor (CFTR potentiator)	Cystic Fibrosis (rare molecular variants)	CF Foundation Patient Registry[1,2]	Label expansions to rare genetic variants
Carglumic Acid (CPS-1 Activator)	NAGS deficiency	Disease registry with natural history data[1]	Orphan approval

Key Findings

- RWE is transitioning from supplementary to foundational in the regulatory decision-making process for precision medicine **(Table 1)**
- Disease registries enabled therapy expansion to ultra-rare genetic disorders through longitudinal outcomes **(Table 1)**
- Data quality remains the rate-limiting step for regulatory acceptance
- Hybrid evidence frameworks accelerate patient access while maintaining scientific rigor **(Figure 1)**

Future Directions

- **Harmonized data interoperability standards, frameworks, and regulatory guidance** across health systems and countries to enable larger observational studies[2]
- **Advanced causal inference methods** to mitigate unmeasured confounding when utilizing RWD sources.
- **Leveraging RWD** from diverse care settings to address evidence gaps and promote equitable health information access.

Conclusions

- RWE is evolving to become foundational in precision medicine regulatory pathways, particularly for rare diseases & biomarker-driven indications.
- Hybrid evidence frameworks combining trial rigor with real-world breadth enable expanded regulatory decision-making while maintaining strict methodological standards.
- RWE validates study findings across broader populations and extends indications to non-studied molecular variants.
- RWE methodologies must continue advancing to consistently achieve the rigor and reproducibility required to meet evolving regulatory standards.

References:

1. Nagel, E., & Roman, Y. M. (2026). The role of real-world data and real-world evidence in advancing regulatory science and targeted therapeutics: a narrative review from the United States perspective. *Personalized Medicine*, 1-8.
2. Alipour-Haris, G., Liu, X., Acha, V., Winterstein, A. G., & Burcu, M. (2024). Real-world evidence to support regulatory submissions: a landscape review and assessment of use cases. *Clinical and Translational Science*, *17*(8), e13903.
3. Marcus, L., Fashoyin-Aje, L. A., Donoghue, M., Yuan, M., Rodriguez, L., Gallagher, P. S., ... & Lemery, S. J. (2021). FDA approval summary: pembrolizumab for the treatment of tumor mutational burden–high solid tumors. *Clinical Cancer Research*, *27*(17), 4685-4689.
4. Sledge Jr, G. W., Yoshino, T., Xiu, J., Helmstetter, A., Ribeiro, J. R., Klimov, S., ... & Spetzler, D. (2025). Real-world evidence provides clinical insights into tissue-agnostic therapeutic approvals. *Nature Communications*, *16*(1), 2646.

Disclosure: This analysis has been published by the authors and can be read at: https://doi.org/10.1080/17410541.2026.2655298

Funding: This work was partly supported by the National Institute of General Medical Sciences [1P20GM155898-01A1]