Paper RE15

Leveraging Real-World Evidence (RWE) in Clinical Trial Design: Statistical Challenges and Opportunities

Muhammed Farzan K, Pfizer Healthcare India Pvt Ltd, Chennai, India

ABSTRACT

The integration of Real-World Evidence (RWE) into clinical trial design enhances generalizability, accelerates timelines, and supports regulatory decision-making. However, RWE introduces statistical challenges, including confounding, selection bias, and data heterogeneity, which may compromise validity. This abstract outlines methodologies to address these challenges:

1. Propensity Score Matching: Mitigates selection bias by balancing treatment groups.
2. Causal Inference Frameworks: Ensures robust causal conclusions from observational data.
3. Bayesian Hierarchical Models: Handles data heterogeneity across diverse populations.

We explore opportunities for optimizing control arms using RWD, refining eligibility criteria, and enabling external control studies. Advances in RWD collection and harmonization are making RWE increasingly feasible for regulatory-grade trials. Strategic integration of RWE into clinical trials enables research to mirror real-world patient outcomes, improving efficiency and relevance. This paradigm shift necessitates collaboration across statisticians, clinicians, and regulators to deliver robust, patient-centric evidence that aligns with evolving healthcare needs and regulatory standards.

INTRODUCTION

Traditional Randomised Controlled Trials (RCTs) have long been considered the "gold standard" for establishing the safety and efficacy of medical interventions. However, RCTs are often expensive, time-consuming, and conducted within homogenous populations using restrictive criteria, which can limit their external validity or generalisability to broader real-world populations.

Real-World Data (RWD) are defined as data relating to patient health status or healthcare delivery routinely collected from various sources, such as electronic health records (EHRs), medical claims, and product registries. Real-World Evidence (RWE) is the clinical evidence derived from the analysis of this data. Driven by legislation such as the 21st Century Cures Act, regulatory bodies like the FDA are increasingly creating frameworks to evaluate how RWE can support drug approvals and help bring breakthrough therapies to patients faster.

STATISTICAL CHALLENGES

The lack of randomization in RWD presents significant hurdles for establishing causal relationships. The primary challenges include:

1. CONFOUNDING AND SELECTION BIAS

Since treatment is not randomly assigned, real-world patients often differ systematically from trial participants in ways that influence outcomes.

2. DATA HETEROGENEITY

RWD often exhibits significant variability due to different medical practices, diagnostic criteria, and data collection methods across various healthcare systems.

3. UNMEASURED CONFOUNDERS

Even with adjustment for measured covariates, unobserved factors such as physician preference or patient health behaviors can influence outcomes.

4. TEMPOROL BIAS

Changes in the standard of care over time can make historical RWD less relevant for comparisons with contemporary trial data.

METHODOLOGICAL FRAMEWORKS

To produce high-quality RWE, statisticians employ several robust frameworks.

PROPENSITY SCORE METHODS

Propensity Score (PS) methodology is a cornerstone for reducing bias in non-randomized studies. A propensity score is the conditional probability of a patient receiving a specific treatment based on their baseline characteristics.

Redefining the Propensity Score In hybrid clinical trials, the PS is often redefined to model the probability of a patient being in the prospective trial versus the external RWD source. This allows researchers to balance characteristics between "traditional" patients and "external" patients.

Standard Techniques The three main ways to use PS are:

- Matching: Finding real-world patients with similar scores to trial participants.
- Stratification: Grouping patients into layers (often five strata) based on their scores to ensure equal distribution of characteristics.
- Weighting (IPTW): Assigning weights to patients to create a "pseudo-population" where treatment groups are comparable.

The 2-Stage Outcome-Free Design To protect study integrity, a two-stage design is recommended. In the first stage, the PS model and patient selection are finalized using only covariate data, without looking at outcomes. Only after the design is agreed upon are the outcomes analyzed in the second stage.

CAUSAL INFERENCE FRAMEWORKS

Establishing "cause and effect" requires a structured approach known as the Causal Roadmap. This framework ensures that observational data can emulate the rigor of a randomized trial.

Key Steps of the Roadmap

1. Define the Causal Estimand: Clearly state the population, treatment strategies, and endpoints using ICH E9(R1) principles.
2. Assess Identifiability: Determine if the observed data are sufficient to answer the causal question.
3. Target Trial Emulation: Design the study to mimic a hypothetical trial, which helps prevent issues like immortal time bias.
4. Sensitivity Analysis: Quantify the "causal gap”, the potential bias introduced by unmeasured factors, to see if it would change the study’s conclusions.

BAYESIAN HIERARCHICAL AND DYNAMIC BORROWING

Bayesian methods provide a flexible way to "borrow" information from external data to strengthen a trial’s conclusions.

Bayesian Additive Regression Trees (BART) BART is a non-parametric model that naturally adjusts for many patient-level variables. It is particularly effective at capturing complex, non-linear relationships and identifying heterogeneous treatment effects across different data sources. Unlike traditional linear models, BART does not require researchers to pre-specify the "shape" of the relationship between variables.

Dynamic Borrowing and ProPP Researchers use a Power Prior parameter (α) to control how much weight to give external data.

• α=0 effectively ignores the external data.

• α=1 fully pools the data.

ProPP (Propensity-score weighted Power Prior) is a novel method that first uses PS weighting to fix measured imbalances and then applies power priors to handle remaining unmeasured confounding.

REGULATORY PERSPECTIVE

The regulatory landscape surrounding Real-World Evidence (RWE) is evolving, with agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) gradually recognizing RWE's role in supporting drug development and approval processes.

FDA's Real-World Evidence Program:

The FDA has initiated its Real-World Evidence Program, focusing on evaluating how RWE can support regulatory decisions. This program is designed to understand how data from outside traditional clinical trials (such as electronic health records and medical claims data) can be utilized in regulatory decision-making.

According to the FDA's Framework for Real-World Evidence Program (2018), RWE can be used for:

- Support in regulatory decisions, including drug approvals.
- Post-market surveillance and assessing long-term safety and effectiveness.
- Extrapolating results from smaller or less diverse clinical trials to broader patient populations.

The FDA emphasizes that RWE can enhance the speed and efficiency of drug approvals and ensure patient-centric evidence. However, the FDA also states that RWE is not a replacement for randomized controlled trials (RCTs), but rather a complementary tool, especially in situations where traditional trials are not feasible due to ethical, logistical, or cost constraints.

EMA's Perspective on RWE:

The EMA also encourages the use of RWE, particularly in cases involving rare diseases or expanded access programs, where traditional clinical trials might be difficult to conduct. The EMA's reflection paper on regulatory uses of RWE highlights its growing importance in observational studies and post-market surveillance, urging the inclusion of RWE in drug development frameworks.

ETHICAL CONSIDERATION

While RWE offers several advantages, its integration into clinical trials raises important ethical concerns, particularly regarding data privacy, informed consent, and bias in observational data.

- Informed Consent: In RWE studies, particularly those using retrospective data from health records, informed consent can be a challenge. Patients might not have explicitly consented to the use of their data for research purposes. To mitigate this, researchers often rely on secondary use of anonymized data, but this raises concerns about privacy breaches. Ethical guidelines stress the importance of data anonymization and the need for robust data security measures to protect patient identities.

- Bias in Data: RWE can suffer from selection bias and confounding, which can distort the true effects of treatments. These biases are more pronounced in observational studies than in randomized controlled trials, where randomization helps eliminate such issues. Ethical challenges arise in ensuring that the evidence derived from RWE is valid and not misleading, especially in regulatory decisions that could impact patient safety.

OPPORTUNITY IN TRIAL DESIGN

The strategic use of RWE offers several advantages for drug development:

External Control Arms (ECA) In rare disease research where randomization may be unethical or impossible, RWD can serve as a synthetic control group. This allows single-arm trials to be contextualized against the natural progression of the disease.

Hybrid Control Approaches Instead of purely external control, researchers can augment a small trial control group with RWD to increase statistical power while reducing the number of patients assigned to placebo.

Broadening Trial Reach RWE allows for the inclusion of diverse populations, such as those in Expanded Access or compassionate use programs, who are typically excluded from traditional RCTs due to illness or age.

FUTURE DIRECTION

The future of RWE is likely to be shaped by technological advances and improvements in data collection and analysis techniques. Key trends include:

- AI and Machine Learning: Machine learning algorithms are becoming essential in analyzing large volumes of real-world data. These tools can help identify patterns, predict outcomes, and adjust for confounding factors that might not be captured in traditional statistical models. Advanced AI techniques such as natural language processing (NLP) can also extract meaningful insights from unstructured data, like clinical notes or social media posts, further enhancing RWE analysis.

- Blockchain for Data Integrity: One emerging technology is blockchain, which can provide secure, transparent, and immutable records of real-world data. This can address concerns about data manipulation or discrepancies between datasets from various sources. Blockchain ensures that the data used in clinical trials is verifiable and trustworthy, which is crucial for regulatory purposes.

- Wearables and Digital Health: Devices like wearables and mobile health applications are increasingly used to collect real-time data from patients, further expanding the scope of RWE. These technologies enable continuous monitoring of patient health, providing high-resolution data that can improve clinical trial outcomes. This also opens the door for more personalized medicine, as treatments can be tailored based on individual patient data collected in real-time.

CASE STUDIES

Several case studies demonstrate the successful application of RWE in clinical trial designs:

- The Use of External Control Arms in Oncology Trials: In oncology, external control arms (ECA) have been successfully used in single-arm trials where randomization is not feasible. For example, in the development of CAR-T cell therapies, RWE from historical data and external databases was used to contextualize trial results, allowing researchers to demonstrate the effectiveness of the treatment without a randomized control group.

- Rare Disease Trials: In rare diseases, where enrolling enough participants for a traditional RCT is challenging, RWE is often used as a synthetic control group. One example is the MPS II trial (Hunter Syndrome), where data from registries and clinical records was used to provide external control for the study. This helped provide insights into the natural disease course and evaluate the effectiveness of the investigational drug.

CHALLENGES AND LIMITATIONS OF RWE INTEGRATION

Despite its potential, integrating RWE into clinical trials poses several challenges:

- Data Quality and Consistency: Data collected from different healthcare systems may have inconsistent definitions, missing values, or varied formats, making it difficult to harmonize the data for analysis.

- Regulatory Hurdles: Regulatory agencies are still developing frameworks to evaluate the quality and reliability of RWE, and there is often uncertainty about how RWE can be integrated into approval processes, particularly for new drugs and innovative treatments.

- Statistical Complexity: While methodologies like propensity score matching and Bayesian modeling help address confounding, the statistical methods required to properly adjust for biases and confounding factors in RWE are complex and require expertise to implement correctly.

CONCLUSION

The integration of Real-World Evidence (RWE) into clinical trial design represents a transformative shift towards more patient-centric and efficient drug development. Traditional Randomized Controlled Trials (RCTs) have long been considered the gold standard for establishing the safety and efficacy of medical interventions. However, their limitations, such as inflated costs, extended timelines, and restricted patient eligibility, have sparked the need for alternatives. RWE, derived from routinely collected data such as electronic health records and registries, offers a significant opportunity to address these challenges. It promises faster drug development, greater generalizability of trial results,

and a more accurate reflection of real-world patient outcomes. However, the use of RWE in clinical trials is not without its difficulties, particularly with respect to confounding, selection bias, and data heterogeneity. Advanced statistical methodologies, including propensity score matching, causal inference frameworks, and Bayesian hierarchical models, are essential for overcoming these challenges and ensuring that conclusions drawn from observational data remain valid.

The increasing recognition of RWE by regulatory agencies, such as the FDA and EMA, further emphasizes its potential to accelerate drug approvals, especially in cases where traditional trials may be ethically or logistically impractical. However, the integration of RWE into regulatory frameworks presents both opportunities and challenges. While RWE can support faster approvals, it also requires careful attention to data quality, consistency, and ethical standards. Ethical concerns around data privacy, informed consent, and biases inherent in observational data must be addressed. As such, stakeholders, including statisticians, clinicians, and regulators, must collaborate to establish clear guidelines for the responsible use of RWE in clinical research, ensuring that patient confidentiality is maintained and that the data used is reliable and unbiased.

Looking ahead, technological advancements such as artificial intelligence, machine learning, and blockchain have the potential to further enhance the ability to analyze and integrate real-world data. Emerging tools like wearables and mobile health applications will allow for real-time data collection, further enabling personalized medicine and improving trial design. Despite these innovations, challenges in data quality, statistical complexity, and regulatory acceptance will continue to pose barriers. Continued collaboration across disciplines will be crucial for addressing these challenges. As the field evolves, RWE is set to become a cornerstone of modern clinical trial design, offering a more adaptive, efficient, and patient-focused approach to drug development and regulatory decision-making.

REFERENCES

Burcu, M., Dreyer, N. A., Franklin, J. M., Blum, M. D., Critchlow, C. W., Perfetto, E. M., & Zhou, W. (2020). Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms. Pharmacoepidemiology and Drug Safety, 29(10), 1228–1235. https://doi.org/10.1002/pds.4975

Dang, L. E., Gruber, S., Lee, H., Dahabreh, I. J., Stuart, E. A., Williamson, B. D., Wyss, R., Díaz, I., Ghosh, D., Kıcıman, E., Alemayehu, D., Hoffman, K. L., Vossen, C. Y., Huml, R. A., Ravn, H., Kvist, K., Pratley, R., Shih, M.-C., Pennello, G., . . . Petersen, M. (2023). A causal roadmap for generating high-quality real-world evidence. Journal of Clinical and Translational Science, 7(1), e212. https://doi.org/10.1017/cts.2023.635

Happich, M., Brnabic, A., Faries, D., Abrams, K., Winfree, K. B., Girvan, A., Jonsson, P., Johnston, J., Belger, M., & IMI GetReal Work Package 1. (2020). Reweighting randomized controlled trial evidence to better reflect real life – A case study of the Innovative Medicines Initiative. Clinical Pharmacology & Therapeutics, 108(4), 811–820. https://doi.org/10.1002/cpt.1854

Li, H., & Yue, L. Q. (2023). Propensity score-based methods for causal inference and external data leveraging in regulatory settings: From basic ideas to implementation. Pharmaceutical Statistics, 22(4), 564–577. https://doi.org/10.1002/pst.2294

Nomura, S., Ohigashi, T., & Sawamoto, R. (2022). Design and analysis of randomized controlled trials using a hybrid control approach: A case when external data is derived as summary statistics. Japanese Journal of Biometrics, 43(1), 63–96.

Polak, T. B., Labrecque, J. A., Uyl-de Groot, C. A., & van Rosmalen, J. (2023). Augmenting treatment arms with external data through propensity-score weighted power-priors: An application in expanded access [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2306.01557

Schuster, V., & Marco, A. T. (2024). Real-world evidence requirements with respect to external control arms of single-arm clinical trials by major regulatory and HTA agencies – Comparative review of guidelines and identification of trends based on seven recent case studies. Biomedical Journal of Scientific & Technical Research, 58(1), 49952–49966. https://doi.org/10.26717/BJSTR.2024.58.009096

U.S. Food and Drug Administration. (2018). Framework for FDA's real-world evidence program. https://www.fda.gov/media/120060/download

Yap, T. A., Jacobs, I., Baumfeld Andre, E., Lee, L. J., Beaupre, D., & Azoulay, L. (2022). Application of real-world data to external control groups in oncology clinical trial drug development. Frontiers in Oncology, 11, 695936. https://doi.org/10.3389/fonc.2021.695936

Zhou, T., & Ji, Y. (2021). Incorporating external data into the analysis of clinical trials via Bayesian additive regression trees [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2103.08754

OpenAI. (2025). ChatGPT (version 5.2) [AI model]. OpenAI. https://openai.com

Google. (2025). Google NotebookLM. https://notebooklm.google/

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my leadership team for providing me with the opportunity to work and present this topic. I am especially thankful to my managers, Nisha Narayanan Iyer, and Vikram Venugopal, for their continuous guidance, encouragement, and support throughout the development of this work.

I would also like to extend my sincere thanks to PHUSE for providing a platform that fosters knowledge sharing, collaboration, and professional growth within the global data science and clinical programming community.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:
Author Name: Muhammed Farzan K
Company: Pfizer Healthcare India Pvt Ltd
Address: New No.237, Anna Salai, Thousand Lights, Chennai, Tamil Nadu 600014, India
Email: muhammedfarzan.k@pfizer.com
Website: www.linkedin.com/in/muhammed-farzan-k-08768a1b6