Editorial | Journal of Orthopaedic Case Reports 2025 October:15(10):Page 6-9

Real-World Evidence: Methodologies for Integrating Real-World Data into Clinical Research Frameworks

Sachin Kale[1], Arvind Vatkar[2], Ojasv Gehlot[1], Ashok Shyam[3,4]

Learning Point of the Article:

What to Learn from this Article- This article highlights how real-world evidence (RWE), drawn from real-world data, is reshaping clinical research by complementing randomized controlled trials. It underscores both opportunities-personalized care, broader insights, regulatory support—and challenges like data quality, bias, and privacy. Collaboration, advanced analytics, and ethical frameworks are essential for meaningful, patient-centered application.

Abstract

Real-world evidence (RWE), derived from real-world data (RWD), is transforming clinical research by complementing traditional randomized controlled trials. With diverse data sources such as electronic health records, patient registries, and wearable devices, RWE offers insights that reflect everyday clinical practice. Despite challenges like unstructured data, bias, and privacy concerns, advances in artificial intelligence, machine learning, and data standardization enable meaningful analysis. Regulatory frameworks, including India's Digital Personal Data Protection Act, reinforce ethical use of patient data. By refining methodologies and fostering collaboration, RWE provides valuable evidence for regulatory decisions, personalized medicine, and enhanced patient care outcomes.

Keywords: Real-world evidence, Real-world data, Clinical research, Artificial intelligence, Personalized medicine

Introduction

In the rapidly evolving field of clinical research, traditional methodologies centered around randomized controlled trials (RCTs) have long been considered the gold standard for generating evidence [1]. However, with advanced data collection and analytical technologies, real-world evidence (RWE) integration is emerging as a powerful complement to traditional methods [2]. RWE, derived from real-world data (RWD), has the potential to revolutionize clinical research frameworks, providing insights that are more representative of everyday patient experiences.

The Rise of RWE

RWE refers to clinical evidence regarding the usage, benefits, and risks of medical products derived from the analysis of RWD [2, 3]. RWD encompasses various data sources, including electronic health records, claims and billing activities, patient registries, operative notes, patient examination forms, wearable devices, and even social media platforms [4]. Even heart rate and blood pressure measures made by nurses in clinics and hospitals are considered RWD. The increasing availability and granularity of such data, coupled with advancements in data science, have paved the way for RWE to play a critical role in regulatory decision-making, post-market surveillance, and personalized medicine [5].

Access this article online

Website: www.jocr.co.in

DOI: https://doi.org/10.13107/jocr.2025.v15.i10.6138

Author's Photo Gallery


Dr. Sachin Kale


Dr. Arvind Vatkar


Dr. Ojasv Gehlot


Dr. Ashok Shyam

[1]Department of Orthopaedics, Dr D Y Patil School of Medicine, Nerul, Navi Mumbai, India,
[2]Department of Orthoapedics, MGM Medical College, Nerul, Navi Mumbai, Maharashtra, India
[3]Indian Orthopaedic Research Group, Thane, Maharashtra, India,
[4]Department of Orthopaedics, Sancheti Institute for Orthopaedics and Rehabilitation, Pune, Maharashtra, India.

Address of Correspondence:
Dr. Sachin Kale,
Department of Orthopaedic, Dr D Y Patil School of Medicine, Nerul, Navi Mumbai, India.
E-mail: sachinkale@gmail.com

Submitted: 90/07/2025; Review: 07/08/2025; Accepted: September 2025; Published: October 2025

DOI: https://doi.org/10.13107/jocr.2025.v15.i10.6138

When comparing RWD to evidence-based research, RWD looks chaotic. It is valuable and full of clinical information but has not been carefully compiled. Data sets may have missing information and many confounding variables for patients. However, there's plenty of it [6,7]. This data were previously considered unusable because there were no technological advances, such as big data and artificial intelligence (AI) to draw valuable conclusions from this vast volume of random data. However, this data may now be collected and analyzed to draw meaningful conclusions [8]. It's like extracting gold, copper, and other valuable metals from a mound of electrical garbage. If done correctly, it can revitalize existing research, particularly in countries, such as India, where 1.4 billion people receive various medical treatments. However, this information is never recorded or capitalized on due to a lack of systematic data collection methodologies.

Now, let's understand the pros and cons of RWD.

Pros of RWE

1. Provides more diversified patient insights

2. Captures actual clinical practice settings

3. Enables understanding of therapy efficacy across different populations

4. Promotes precision medicine and comparative effectiveness studies [9, 10].

Challenges and disadvantages

1. Data management challenges include unstructured and potentially inconsistent data, necessitating advanced machine learning (ML) and natural language processing (NLP) approaches [2, 11]

2. Increased likelihood of bias and misleading findings [12]

3. To obtain valuable insights, robust methodological procedures are required [13].

Methodologies for Integrating RWE into Clinical Research

Integrating RWE into clinical research frameworks requires robust methodologies to ensure data reliability, validity, and relevance. Below, we explore key approaches:

Data collection and curation

The foundation of reliable RWE lies in the quality of RWD. This involves:

• Data standardization: Ensuring consistent formats and terminologies across datasets using standards, such as HL7 Fast Healthcare Interoperability Resources or Clinical Data Interchange Standards Consortium [14].

• Data cleaning: Addressing missing, incomplete, or erroneous data points through rigorous cleaning processes

• Data integration: Combining disparate datasets to view patient outcomes comprehensively [14,15].

Study design adaptations

Unlike RCTs, which rely on controlled environments, RWE studies must adapt to the complexities of real-world settings. Hence, we must do slightly lower-level research [13] which can later form the basis for larger datasets based systematic reviews and meta-analyses. Standard study designs include:

• Cross-sectional studies - Prevalence studies, case series of specific disorders or surgical techniques [16]

• Retrospective cohort studies: Leveraging historical data to study patient outcomes over time [17]

• Case–control studies: To identify contributing factors, comparing patients with a specific outcome to those without [18]

• Hybrid studies: Combining elements of RCTs and observational studies to validate findings across diverse contexts [19]

Advanced analytical techniques

Analyzing RWD requires sophisticated methodologies to handle its volume, variety, and velocity. Techniques include:

• ML and AI: Using ML algorithms to detect patterns, predict outcomes, and identify risk factors [20]

• Propensity score matching: Reducing selection bias by matching patients with similar baseline characteristics [21]

• NLP: Extracting meaningful information from unstructured data sources, such as physician notes and social media posts [22].

Regulatory considerations

India passed the Digital Personal Data Protection Act in August 2023, creating a comprehensive framework for securing personal data, including medical information. The Act requires organizations to acquire consent before processing data and to use reasonable security measures to prevent breaches. It applies to digital personal data gathered within India's borders but not non-digital data. For RWE to be impactful, it must align with regulatory standards [23]. Agencies outside India, such as the Food and Drug Administration and European Medicines Agency, have issued guidelines emphasizing:

• Transparency: Clear documentation of methodologies and

assumptions

• Reproducibility: Ensuring independent researchers can replicate findings

• Patient privacy: Adhering to stringent data protection regulations, such as the General Data Protection Regulation and Health Insurance Portability and Accountability Act [24].

Stakeholder collaboration

Integrating RWE requires collaboration across a broad ecosystem, including:

• Healthcare providers: Contributing clinical insights and facilitating data collection

• Patients: Sharing real-world experiences through patient-reported outcomes

• Industry players: Partnering to develop infrastructure and tools for RWD analysis [25].

Challenges and Opportunities

Despite its promise, the integration of RWE faces several challenges:

• Data quality and bias: Ensuring data integrity while mitigating biases inherent in observational studies

• Interoperability issues: Overcoming technical barriers to integrate diverse data sources

• Ethical concerns: Addressing privacy and consent issues in using personal health data [26].

However, the opportunities are immense. By capturing a broader spectrum of patient experiences, RWE can:

• Enhance the understanding of rare diseases and diverse patient populations

• It helps to understand local outbreaks of diseases in specific localities, such as lead poisoning near a chemical factory and congenital deformity rates near a radioactive excavation site, etc.

• Inform real-time decision-making in clinical settings

• Support adaptive trial designs and expedite drug approvals.

Conclusion

Integrating RWE into clinical research frameworks represents a paradigm shift in evidence generation. By embracing innovative methodologies, fostering cross-sector collaboration, and addressing inherent challenges, the healthcare industry can unlock the full potential of RWE. As traditional research boundaries expand, RWE stands poised to deliver statistically significant insights that are profoundly impactful in improving patient care.

Clinical Message

RWE enriches clinical research by capturing patient experiences beyond controlled trial settings. Effective integration requires robust methodologies, data standardization, and adherence to ethical regulations. With advanced analytics and stakeholder collaboration, RWE can guide precision medicine, improve regulatory decisions, and strengthen patient-centric healthcare in diverse real-world contexts.

References

1. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: Randomised controlled trials. BJOG 2018;125:1716.

2. Liu F, Panagiotakos D. Real-world data: A brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol 2022;22:287.

3. Levenson M, He W, Chen J, Fang Y, Faries D, Goldstein BA, et al. Biostatistical considerations when using RWD and RWE in clinical studies for regulatory purposes: A landscape assessment. Stat Biopharm Res 2021;15:3-13.

4. Dang A. Real-world evidence: A primer. Pharmaceut Med 2023;37:25-36.

5. Li P, Wang S, Chen Y. Use of real-world evidence in regulatory decisions for traditional Chinese medicine: Current status and future directions. Ther Innov Regul Sci 2024;58:34-41.

6. Hernández MA, Stolfo SJ. Real-world data is dirty: Data cleansing and the merge/purge problem. Data Min Knowl Discov 1998;2:9-37.

7. Zhang X, Stamey JD, Mathur MB. Assessing the impact of unmeasured confounders for credible and reliable real-world evidence. Pharmacoepidemiol Drug Saf 2020;29:1219-27.

8. Sarker IH. Machine learning: Algorithms, real-world applications and research directions. SN Comput Sci 2021;2:160.

9. Sun F, Bedenkov A, Liu BC, Yang J, Xu JF, Ji L, et al. Maximizing the value of real-world data and real-world evidence to accelerate healthcare transformation in China: Summary of external advisory committee meetings.

Pharmaceut Med 2024;38:157-66.

10. Liao X, Yao C, Zhang J, Liu LZ. Recent advancement in integrating artificial intelligence and information technology with real-world data for clinical decision-making in China: A scoping review. J Evid Based Med 2023;16:534-46.

11. Benedum CM, Sondhi A, Fidyk E, Cohen AB, Nemeth S, Adamson B, et al. Replication of real-world evidence in oncology using electronic health record data extracted by machine learning. Cancers (Basel) 2023;15:1853.

12. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. N Engl J Med 2020;382:674-8.

13. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence - what is it and what can it tell us? N Engl J Med 2016;375:2293-7.

14. Ueno S, Komiyama Y, Doi M, Hoshi K. Need for data standardization and infrastructure of research data management to promote using real-world data. Digital First 2024;???:???.

15. Guo M, Wang Y, Yang Q, Li R, Zhao Y, Li C, et al. Normal workflow and key strategies for data cleaning toward real-world data: Viewpoint. Interact J Med Res 2023;12:e44310.

16. Fang Y, He W, Wang H, Wu M. Key considerations in the design of real-world studies. Contemp Clin Trials 2020;96:106091.

17. Loucera C, Carmona R, Esteban-Medina M, Bostelmann G, Muñoyerro-Muñiz D, Villegas R, et al. Real-world evidence with a retrospective cohort of 15,968 COVID-19 hospitalized patients suggests 21 new effective treatments. Virol J 2023;20:226.

18. Irony TZ. Case-control studies: Using "real-world" evidence to assess association. JAMA 2018;320:1027-8.

19. Zhu M, Sridhar S, Hollingsworth R, Chit A, Kimball T, Murmello K, et al. Hybrid clinical trials to generate real-world evidence: Design considerations from a sponsor's perspective. Contemp Clin Trials 2020;94:105856.

20. Rubinger L, Gazendam A, Ekhtiari S, Bhandari M. Machine learning and artificial intelligence in research and healthcare. Injury 2023;54 Suppl 3:S69-73.

21. Allan V, Ramagopalan SV, Mardekian J, Jenkins A, Li X, Pan X, et al. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. J Comp Eff Res 2020;9:603-14.

22. Loscertales J, Abrisqueta-Costa P, Gutierrez A, Hernández-Rivas JÁ, Andreu-Lapiedra R, Mora A, et al. Real-world evidence on the clinical characteristics and management of patients with chronic lymphocytic leukemia in spain using natural language processing: The SRealCLL study. Cancers (Basel) 2023;15:4047.

23. Sundara K, Narendran N. The digital personal data protection act, 2023: Analysing India's dynamic approach to data protection. Comput Law Rev Int 2023;24:129-41.

24. Bhatt A. Ethical considerations for real-world evidence studies. Perspect Clin Res 2024;15:152-4.

25. Wise J, Möller A, Christie D, Kalra D, Brodsky E, Georgieva E, et al. The positive impacts of real-world data on the challenges facing the evolution of biopharma. Drug Discov Today 2018;23:788-801.

26. Lipworth W. Real-world data to generate evidence about healthcare interventions: The application of an ethics framework for big data in health and research. Asian Bioeth Rev 2019;11:289-98.

Conflict of Interest: Nil
Source of Support: Nil

Consent: The authors confirm that informed consent was obtained from the patient for publication of this case report

How to Cite this Article

Kale S, Srivastava S, Vatkar A, Gehlot O. Real-World Evidence: Methodologies for Integrating Real-World Data into Clinical Research Frameworks. Journal of Orthopaedic Case Reports 2025 October;15(10):06-09.