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Real World Evidence as a Transformative Force in Evidence Based Medicine Reconciling External Validity Regulatory Science and Clinical Decision Making in the Big Data Era

[1] Dr. Mias Montverde
[1] Universidad Nacional de Rosario, Argentina

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Abstract

The contemporary practice of medicine stands at a pivotal crossroads in which the long dominant paradigm of evidence based medicine built primarily upon randomized controlled trials is being challenged by the growing availability, sophistication, and regulatory acceptance of real world data and real world evidence. This shift is not merely technical but epistemological, redefining what counts as valid knowledge, how uncertainty is handled, and how healthcare decisions are made in complex real life clinical environments. Evidence based medicine emerged as a corrective to intuition driven and authority based practice, yet over time it has faced increasing criticism for privileging methodological purity over clinical relevance, for excluding patients with comorbidities, and for producing results that are often difficult to translate into everyday care. Real world evidence has risen in response to these limitations, offering insights derived from routine clinical practice, electronic health records, insurance claims, registries, and patient reported outcomes. This article develops a comprehensive theoretical and empirical analysis of how real world evidence is reshaping evidence based medicine across clinical, regulatory, and payer decision making contexts. Drawing strictly on the provided references, it explores the philosophical crisis of evidence based medicine, the conceptual foundations of real world data, the evolving regulatory landscape in the United States, Japan, and other advanced systems, and the methodological innovations that enable observational data to approach causal inference. The article also examines pragmatic trials, propensity score methods, and hybrid designs that integrate randomized and observational approaches. Particular attention is given to the external validity problem, which arises when trial populations fail to represent the diversity of real patients, and how real world evidence provides a corrective by capturing heterogeneity, comorbidity, and long term outcomes. The analysis further addresses concerns regarding bias, data quality, and reproducibility, and demonstrates how quality standards, regulatory frameworks, and advanced analytic techniques are being developed to ensure that real world evidence complements rather than undermines scientific rigor. The article concludes that the future of evidence based medicine lies not in abandoning randomized trials but in integrating them within a broader evidence ecosystem in which real world evidence plays an essential and increasingly authoritative role.

Keywords: Real world evidence, evidence based medicine, external validity, regulatory science, pragmatic trials, observational research, health decision making.

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1. Introduction

Evidence based medicine emerged in the late twentieth century as a reform movement aimed at grounding clinical practice in systematically generated scientific knowledge rather than tradition, anecdote, or expert opinion. Its central methodological commitment was the primacy of randomized controlled trials and meta analyses as the

highest form of medical evidence. This hierarchy of evidence was justified by the ability of randomization to eliminate confounding, thereby producing internally valid estimates of treatment effects. However, as Greenhalgh, Howick, and Maskrey argued in their influential critique, evidence based medicine has entered a period of crisis in which its original goals of improving patient care have been undermined by rigid methodological dogma, industrial interests, and a narrowing of what counts as legitimate knowledge (Greenhalgh et al., 2014). The crisis is not simply that trials can be biased or manipulated but that even when perfectly conducted they often fail to address the complexity of real world clinical practice.

One of the central problems identified in this crisis is external validity, meaning the degree to which trial results apply to the populations and settings in which treatments are actually used. Fortin and colleagues demonstrated that patients with multiple comorbidities, who represent a substantial proportion of those seen in primary care, are systematically excluded from most randomized controlled trials, rendering the resulting evidence less relevant to those who need it most (Fortin et al., 2006). Tan and colleagues further quantified this representativeness gap on an unprecedented scale, showing that across tens of thousands of trials and millions of real world patients, trial populations are often younger, healthier, and less diverse than the populations to whom the drugs are ultimately prescribed (Tan et al., 2022). This mismatch means that even statistically precise estimates of efficacy may be misleading when applied to complex patients in everyday practice.

Real world evidence has emerged as both a critique and a complement to the traditional evidence based medicine paradigm. Real world data, defined as data relating to patient health status and the delivery of healthcare that are routinely collected from a variety of sources, including electronic health records, claims databases, registries, and digital health technologies, provides the raw material for real world evidence (Makady et al., 2017). When these data are analyzed using appropriate scientific methods, they yield evidence about the benefits and risks of medical interventions in routine clinical settings. Unlike randomized trials, which are conducted under controlled conditions, real world evidence reflects the messy, heterogeneous, and often imperfect realities of clinical care.

The growing importance of real world evidence is reflected in regulatory, payer, and clinical decision making. The United States Food and Drug Administration has developed a formal Real World Evidence Program to evaluate how such data can be used to support regulatory decisions about drug and device approval, labeling changes, and post marketing safety monitoring (United States Food and Drug Administration, 2024). Similarly, regulatory authorities in Japan have increasingly incorporated real world evidence into benefit risk assessments, reflecting a global shift toward more flexible and context sensitive forms of evidence (Nishioka et al., 2022). Payers and health technology assessment bodies have also turned to real world evidence to inform coverage and payment decisions, particularly in situations where randomized trial data are limited or do not reflect real use patterns (Malone et al., 2018; Garrison et al., 2007).

Despite this momentum, the integration of real world evidence into evidence based medicine remains contested. Critics argue that observational data are inherently biased, that big data can produce spurious correlations, and that reliance on real world evidence risks lowering the scientific bar. Proponents counter that these concerns can be addressed through rigorous design, analytic methods such as propensity score adjustment, and transparent reporting standards (Kuss et al., 2016; McMurry et al., 2015; Roche et al., 2014). The debate is therefore not about whether real world evidence should replace randomized trials but about how these two forms of evidence can be combined to produce more relevant, trustworthy, and actionable knowledge.

This article aims to provide a comprehensive and theoretically grounded analysis of how real world evidence is transforming evidence based medicine. Using only the references provided, it examines the epistemological foundations of both randomized and observational approaches, the methodological innovations that bridge them, and the regulatory and clinical contexts in which they are applied. By situating real world evidence within the broader crisis and evolution of evidence based medicine, the article seeks to demonstrate that the future of medical knowledge lies in an integrated evidence ecosystem that values both internal and external validity, both control and realism, and both experimental and observational insight.

2. Methodology

The methodological approach of this article is a rigorous narrative synthesis and theoretical integration of the peer reviewed literature and regulatory documents provided in the reference list. Because the task is to generate an original research article based strictly on the supplied sources, the methodology does not involve the collection of new empirical data but rather the systematic interpretation, comparison, and conceptual synthesis of existing scholarly

and policy oriented evidence. This approach is consistent with the tradition of theoretical and methodological research in health services and clinical epidemiology, where advances in practice often arise from the critical examination and integration of existing knowledge rather than from a single new dataset.

The first step in the methodology involved a comprehensive reading and thematic coding of all provided references. Key conceptual domains were identified, including the crisis of evidence based medicine, definitions and sources of real world data, regulatory acceptance of real world evidence, methodological tools for causal inference in observational research, pragmatic trial designs, and the role of real world evidence in clinical and payer decision making. Each reference was then mapped to these domains. For example, Greenhalgh et al. provided the conceptual critique of traditional evidence based medicine, while Makady et al. offered definitional clarity regarding real world data. Regulatory perspectives were drawn from FDA documents and from Nishioka et al., while methodological issues were informed by Kuss et al., McMurry et al., and Roche et al.

The second step consisted of constructing a theoretical framework that links these domains into a coherent narrative about the evolution of evidence based medicine. This framework treats evidence not as a static hierarchy but as a dynamic ecosystem in which different forms of data and study designs serve different but complementary purposes. Within this framework, randomized controlled trials are understood as optimizing internal validity and causal attribution, while real world evidence is understood as optimizing external validity and contextual relevance. This conceptualization draws on the work of Booth and Tannock, who described randomized and observational research as partners rather than competitors in the evolution of medical evidence (Booth and Tannock, 2014).

The third step involved a critical analysis of methodological rigor in real world evidence studies. Propensity score methods, as described by Kuss et al. and McMurry et al., were examined in detail as tools for addressing confounding in observational data. Quality standards for observational database studies, as articulated by Roche et al., were analyzed to show how transparency, reproducibility, and validity can be ensured even outside randomized designs. These methodological discussions were then integrated with regulatory and clinical perspectives, such as those of Dreyer and Sherman et al., to demonstrate how methodological rigor translates into practical decision making.

Throughout the analysis, all major claims and interpretations are explicitly grounded in the cited literature, using the author and year citation format. No external sources or speculative claims are introduced. The goal is not merely to summarize the literature but to provide an in depth theoretical elaboration that connects individual findings into a broader understanding of how real world evidence is reshaping the epistemology and practice of medicine.

3. Results

The synthesis of the provided literature yields several interrelated findings that together demonstrate the transformative impact of real world evidence on evidence based medicine. These findings can be organized around five major themes: the limitations of traditional randomized controlled trials, the conceptualization and sources of real world data, the regulatory and institutional acceptance of real world evidence, the methodological maturation of observational research, and the practical implications for clinical and payer decision making.

The first major finding is that randomized controlled trials, while indispensable for establishing causal efficacy under controlled conditions, are structurally limited in their ability to inform real world clinical practice. Greenhalgh et al. argued that the dominance of randomized trials has led to a form of methodological reductionism in which complex clinical questions are simplified to fit the trial paradigm, often at the expense of patient centered relevance (Greenhalgh et al., 2014). Fortin et al. provided empirical support for this critique by showing that patients with multiple chronic conditions, who are common in primary care, are rarely included in trials, making it difficult to apply trial results to their care (Fortin et al., 2006). Tan et al. extended this analysis across an enormous dataset, revealing systematic discrepancies between trial populations and real world populations across a wide range of drugs and conditions (Tan et al., 2022). Together, these findings establish that the external validity problem is not marginal but endemic to the current trial based evidence system.

The second major finding concerns the nature and scope of real world data. Makady et al. showed that real world data encompasses a diverse array of sources, including electronic health records, claims data, disease registries, and patient generated data, each with its own strengths and limitations (Makady et al., 2017). Dang further elaborated that real world evidence is not defined by the data source alone but by the analytical process that transforms raw data into scientifically interpretable evidence (Dang, 2023). Rudrapatna and Butte highlighted both the opportunities and challenges inherent in these data, noting that their scale

and granularity enable the study of rare events, long term outcomes, and heterogeneous treatment effects, but also raise issues of data quality, missingness, and bias (Rudrapatna and Butte, 2020). The literature thus converges on a view of real world data as a powerful but methodologically demanding resource.

The third major finding is the growing institutionalization of real world evidence within regulatory and policy frameworks. The FDA Real World Evidence Program and the Sentinel System represent a formal recognition that observational data can contribute to regulatory decision making, particularly for post marketing surveillance and for supporting new indications of approved products (United States Food and Drug Administration, 2019; United States Food and Drug Administration, 2024). Nishioka et al. documented a similar trend in Japan, where regulators increasingly use real world evidence to assess benefit risk profiles in contexts where randomized trials are infeasible or insufficient (Nishioka et al., 2022). These developments indicate that real world evidence is no longer peripheral but central to modern regulatory science.

The fourth major finding is the methodological maturation of observational research. Propensity score methods, as detailed by Kuss et al. and McMurry et al., provide a way to balance treatment groups on observed covariates, thereby approximating some of the benefits of randomization in nonrandomized studies (Kuss et al., 2016; McMurry et al., 2015). Roche et al. established quality standards for observational database studies, emphasizing the importance of clear study protocols, transparent reporting, and sensitivity analyses to assess robustness (Roche et al., 2014). These methodological advances challenge the notion that observational research is inherently inferior, showing instead that with appropriate design and analysis it can yield credible and actionable evidence.

The fifth major finding relates to the practical use of real world evidence in clinical and payer decision making. Blonde et al. showed that practicing clinicians increasingly rely on real world data to understand how treatments perform in populations that resemble their own patients, particularly in chronic diseases such as diabetes (Blonde et al., 2018). Malone et al. and Garrison et al. demonstrated that payers use real world evidence to inform coverage and reimbursement decisions, especially when trial data do not capture utilization patterns, adherence, or comparative effectiveness in routine care (Malone et al., 2018; Garrison et al., 2007). Visvanathan et al. highlighted the untapped potential of observational research to inform oncology practice, where rapid innovation and heterogeneous patient populations make exclusive reliance on trials impractical (Visvanathan et al., 2017).

Taken together, these results indicate that real world evidence is not merely an adjunct to evidence based medicine but a fundamental component of its ongoing evolution. By addressing the external validity gap, providing insights into real use patterns, and supporting regulatory and payer decisions, real world evidence expands the scope and relevance of medical knowledge.

4. Discussion

The findings presented above have profound implications for how evidence is conceptualized, generated, and applied in modern medicine. At a theoretical level, they challenge the traditional hierarchy of evidence that places randomized controlled trials at the top and observational studies at the bottom. While this hierarchy was justified by the need to control for bias and confounding, it fails to account for the equally important need for relevance, representativeness, and contextual understanding. As Greenhalgh et al. argued, evidence based medicine has become overly focused on methodological purity, often at the expense of patient centered care and clinical judgment (Greenhalgh et al., 2014). Real world evidence offers a way to rebalance this equation by providing information about how interventions work in the populations and settings where they are actually used.

One of the central theoretical contributions of real world evidence is its ability to address heterogeneity of treatment effects. Randomized trials typically report average treatment effects across a selected population, but clinicians are rarely treating average patients. They are treating individuals with unique combinations of age, comorbidities, socioeconomic status, and preferences. Real world data, because of its scale and diversity, allows researchers to examine how treatment effects vary across subgroups, thereby supporting more personalized and equitable care (Rudrapatna and Butte, 2020). This is particularly important in chronic diseases and oncology, where patient trajectories are complex and long term outcomes matter as much as short term efficacy (Visvanathan et al., 2017).

The integration of real world evidence into regulatory science also represents a significant epistemological shift. Traditionally, regulatory approval has been based almost exclusively on randomized trials, with observational data relegated to post marketing surveillance. The FDA Sentinel System and Real World Evidence Program signal a recognition that this dichotomy is too rigid for a world of

rapidly evolving therapies, rare diseases, and personalized medicine (United States Food and Drug Administration, 2019; United States Food and Drug Administration, 2024). Nishioka et al. showed that Japanese regulators are similarly embracing real world evidence to inform benefit risk assessments, reflecting a global convergence toward more flexible and adaptive regulatory frameworks (Nishioka et al., 2022). This does not mean that standards are being lowered but that they are being diversified to match the complexity of modern therapeutics.

Methodological rigor remains a central concern in the use of real world evidence. Critics rightly point out that observational studies are vulnerable to confounding, selection bias, and measurement error. However, the literature reviewed here demonstrates that these challenges are being actively addressed through advanced design and analytic techniques. Propensity score methods, for example, allow researchers to create balanced comparison groups that mimic some of the properties of randomized trials, thereby reducing bias in estimated treatment effects (Kuss et al., 2016; McMurry et al., 2015). Quality standards for observational research, as articulated by Roche et al., further ensure that studies are transparent, reproducible, and methodologically sound (Roche et al., 2014). The question is therefore not whether real world evidence can be rigorous but whether it is being conducted according to best practices.

The relationship between randomized and observational research should be understood as complementary rather than antagonistic. Booth and Tannock argued that these two approaches are partners in the evolution of medical evidence, each addressing different questions and limitations (Booth and Tannock, 2014). Randomized trials are unparalleled for establishing causal efficacy under controlled conditions, while real world evidence excels at assessing effectiveness, safety, and utilization in routine practice. Pragmatic trials, which combine elements of both approaches by embedding randomization within real world settings, further blur the boundary and offer a promising path forward (Ford and Norrie, 2016; Sox and Lewis, 2016). These hybrid designs exemplify the emerging evidence ecosystem in which methodological diversity is a strength rather than a weakness.

Despite these advances, important challenges remain. Data quality varies widely across real world sources, with issues of missing data, inconsistent coding, and limited clinical detail posing threats to validity (Rajivlochan, 2015; Rudrapatna and Butte, 2020). Governance, privacy, and interoperability also remain significant obstacles to the full realization of real world evidence. Moreover, the increasing involvement of industry in real world evidence generation raises concerns about conflicts of interest and selective reporting, echoing some of the critiques that have been leveled at randomized trials (Greenhalgh et al., 2014). Addressing these challenges will require continued investment in infrastructure, standards, and independent oversight.

Looking to the future, the integration of real world evidence into evidence based medicine offers the potential for a more learning oriented healthcare system. Dagenais et al. showed how real world evidence can inform drug development and clinical trial design, creating a feedback loop in which observational data guide the questions that are tested in trials and trial results are then evaluated in real world populations (Dagenais et al., 2022). Dreyer described this as a strengthening of evidence based medicine rather than a dilution, as it aligns scientific inquiry more closely with the realities of patient care (Dreyer, 2022). Frieden similarly argued that health decision making must move beyond an exclusive reliance on randomized trials if it is to address complex public health challenges (Frieden, 2017).

In this light, real world evidence should be seen not as a threat to scientific rigor but as an expansion of what rigor means. It demands not only careful control of bias but also careful attention to context, diversity, and real life complexity. By integrating randomized and observational approaches, evidence based medicine can evolve from a narrow hierarchy of methods into a rich and adaptive knowledge system capable of supporting better decisions for patients, clinicians, regulators, and society as a whole.

5. Conclusion

The rise of real world evidence marks one of the most significant transformations in the history of evidence based medicine. Faced with the limitations of randomized controlled trials in terms of external validity, representativeness, and real world relevance, the medical and regulatory communities have increasingly turned to observational data to complement and extend traditional forms of evidence. The literature reviewed in this article demonstrates that this shift is grounded in both practical necessity and methodological innovation. Real world data, when analyzed with rigor and transparency, provides insights into how interventions perform in diverse populations over long periods and under routine conditions that cannot be fully captured by trials alone.

Rather than undermining evidence based medicine, real

world evidence addresses many of its most pressing criticisms. It brings patients with comorbidities, varied backgrounds, and complex care pathways into the evidence base. It informs regulatory and payer decisions in contexts where trials are infeasible or incomplete. It supports clinicians in making decisions that reflect the realities of their practice. At the same time, the continued development of quality standards, analytic methods, and regulatory frameworks ensures that the use of real world evidence is scientifically credible and ethically responsible.

The future of evidence based medicine lies not in choosing between randomized trials and real world evidence but in integrating them into a coherent and dynamic evidence ecosystem. In this ecosystem, different methods answer different questions, and together they provide a more complete and trustworthy foundation for healthcare decision making. By embracing this pluralistic and context sensitive approach, medicine can move beyond the crisis identified by Greenhalgh and colleagues toward a more patient centered, scientifically robust, and socially responsive model of knowledge.

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