FROM DATA TO DECISION: EXAMINING REAL-WORLD DATA ANALYSIS TRENDS

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ABSTRACT

Although vast amounts of Real-World Evidence are available from Electronic Health Records, there is little information on current trends in Real-World Data analysis, thus hindering informed decision-making by healthcare professionals. Real World Evidence includes administrative claims, disease or product registries, patient-generated health data, and other digital health technologies. In this study, we review current and relevant developments, as well as guidelines across different countries, to summarize recent advancements and extract valuable insights from the existing literature on Real-World Evidence.

KEYWORDS

Real-World Evidence, Randomized Controlled Trials, Electronic Health Records

1. INTRODUCTION

The use of Real-World Evidence (RWE) in the initial evaluation of pharmaceuticals' benefits and the assessment of treatment effectiveness is becoming more prevalent. RWE refers to all data from any source that may contribute to more effective health care. As the limited eligibility criteria of traditional Randomized Controlled Trials (RCTs) underscores the importance of examining the translation of RCT findings to real-world settings, the exploration of Real-World Data (RWD) provides valuable context with more inclusive patient populations and representation of typically excluded patients in clinical trials. Even the U.S. Food and Drug Administration (FDA) defines RWE as the clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective). To date, RWE has been incorporated into a variety of regulatory approval procedures to assist with decisions regarding treatment safety, as well as to supplement randomized controlled trials in evaluating treatment effectiveness (Kirchgesner *et al.*, 2022).

2. PROBLEM STATEMENT

Over the past decade, the use of RWE has become increasingly prevalent in drug pre-approval and post-approval processes. However, there is a significant lack of comprehensive guidance on how to link RWE to routine clinical practices and research, posing challenges for healthcare professionals and researchers seeking to fully utilize its potential. Although vast amounts of RWD are available from sources such as Electronic Health Records (EHR), administrative claims, disease or product registries, patient-generated health data, and other digital health technologies, there is little information on current trends in RWD analysis, hindering informed decision-making by healthcare professionals (Derman *et al.*, 2022). In this study, we aim

to review current developments and guidelines for RWE across different countries and summarize recent advancements in related fields to extract valuable insights from existing literature. Our goal is to help increase the implementation of real-world data in clinical practice and research.

3. METHODOLOGY

We conducted a targeted literature review, in PubMed using the following keywords: “real-world evidence”, “real-world data”, “effectiveness study”, and “development and future directions”. Such a strategy allows us to review key RWD/RWE studies, status in various countries, and regulatory guidelines. A total of 39 papers were examined and 6 of them were selected for a detailed evaluation of analysis-treatment effectiveness. In addition, the official websites of six different countries were examined to obtain the latest updates on regulations related to RWE.

3.1 Analysis: Treatment Effectiveness

Numerous studies globally employ real-world evidence to investigate the effectiveness of disease treatments, complementing the limited scope of randomized controlled trials. This approach offers several advantages, including evaluating the accuracy of clinical trial evidence, enhancing the generalizability of treatments used in clinical practice, investigating patient profiles of specific diseases, and analyzing treatment responses based on timeframes. In this review, we summarize treatment effectiveness for various diseases, outlining the methodology and main conclusions. In this way, we aim to understand and characterize the current use of real-world studies and to suggest novel approaches for leveraging real-life data effectively (Table 1).

Table 1. Real-World Evidence Usage in the Assessment of Treatment Effectiveness

First Author, Year	Agent	Study Focus	Disease Type	Study Result	Study insight
(Kuehne *et al.*, 2022)	US, Lilly Research Award Program	Methodological challenges and risk of bias when drawing casual conclusions using RWD, in the context of ovarian cancer	Ovarian Cancer	The "fully simulated trial" yielded a hazard ratio of 1.12 (95% CI: 0.96-1.28), which closely aligned with the reference randomized controlled trial. Immortal time bias is a significant source of bias that can impact the effect estimate in different directions.	This study offers guidelines for conducting causal analyses with real-world data and evaluates the effects of biases and confounding factors, such as time-independent and time-dependent confounding, selection bias, and immortal time bias. By employing causal frameworks, researchers can mitigate self-inflicted biases. Additionally, this study suggests that residual (unmeasured) confounding may have less impact on bias than previously thought in real-world data analyses.
(Kirchgesner *et al.*, 2022)	US, Clinical Pharmacology a Therapeutics, Brigham and Women's Hospital and Harva Medical School	Emulate the SONIC trial's findings on the efficacy of infliximab in Crohn's disease patients by utilizing healthcare claims data from the US and France.	Crohn’s disease	Combination therapy reduced the risk of treatment failure in the overall cohort, consistent with the SONIC trial. Patients starting combination therapy had a 29% lower risk of treatment failure than those starting infliximab monotherapy. The study result was consistent across the three databases.	This study utilized real-world data to replicate the efficacy of combination therapy with two drugs in an RCT trial, providing strong evidence that real-world evidence analysis can complement the evidence obtained from RCTs by including patients who are generally excluded from RCTs and defining new outcome measures to improve treatment generalizability.
(Juarez-Garcia *et al.*, 2022)	Bristol Myers Squibb	Overview of the existing real-world evidence regarding the effectiveness of immunotherapy as a second or later treatment option for advanced non-small cell lung cancer in terms of patient survival.	Non-small cell lung cancer (NSCLC)	Of 66 RWE studies reviewed, 46 included a nivolumab-specific monotherapy arm. Nivolumab monotherapy showed higher 1-year and 2-year overall survival rates compared to mixed immune checkpoint inhibitors. Elderly patients and patients with poor performance status had	This study re-evaluated the overall survival rates of immunotherapy observed in clinical trials, using real-world evidence (RWE). The study highlights the advantages of utilizing RWE to analyze treatment effectiveness in vulnerable

				worse survival rates. Nivolumab had lower 2-year overall survival rates in patients with brain metastases than those without.	patient groups often excluded from trials.
(Peng *et al.*, 2022)	China, National Natural Science of China	Literature mining for studies on different clinical tumors and summarizing the antitumor effects of traditional Chinese medicine using real-world data	Common clinical tumors	The real-world clinical application of an integrated treatment approach using traditional Chinese and Western medicine has demonstrated anti-tumor effects regarding overall survival, progression-free survival, mortality hazard ratio, side effects, and medical adherence.	This study is a unique effort to evaluate the efficacy of traditional Chinese medicine by analyzing real-world data. The findings can establish evidence for clinical efficacy improvement and offer insights and cautions for other observational studies that utilize real-world data to determine treatment effectiveness.
(Zhao *et al.*, 2022)	UK, Cancer Research UK RadNet Manchester	Utilize real-world data to study radiation-induced heart disease in patients with lung cancer following radiotherapy and the subsequent change to cardiac dose constraints	Radiation-induced heart disease	An incidental dose to the base of the heart would increase the risk of early mortality in lung cancer patients. High-quality real-world data has the potential to provide robust evidence in the radiation-induced heart disease field by assessing the clinical impact of introducing a new cardiac avoidance region dose constraint as a substitute for traditional RCT.	This study considers the potential of using real-world data to assess dose-treatment effectiveness and corresponding patient survival in postoperative cancer where RCTs are generally impractical. The discussion of ways to achieve high-quality real-world data research in terms of developing auto-segmentation tools and cardiac calcification detection in different phases of the respiratory cycle is also valuable in the development of real-world studies to address cancer disparities.
(Escalera *et al.*, 2022)	Spain	A thorough scoping review of real-world data (RWD) that depicts the characteristics of patients with systemic lupus erythematosus (SLE) who received belimumab in addition to standard care in actual clinical settings in Spain.	Systemic lupus erythematosus	The inclusion of 19 retrospective studies explored the overall prevalence of SLE and the effects of treatment with belimumab on the use of corticoids in Spain. Adding belimumab to standard therapy reduced daily glucocorticoid intake by 1.4–11.1 mg at 6 months. Belimumab discontinuation was observed in 18.6% of patients.	This study demonstrates the potential of real-world data to analyze the clinical characteristics of patients receiving specific treatment. Incorporating long-term retrospective studies to examine treatment effectiveness, offers insights into usage shifts and aids in predicting future trends. This information can be used to identify patient populations that are most likely to benefit from the given drug.

3.2 Regulatory

We examine the regulatory and legislative developments regarding RWE and RWD by leveraging the main legislative frameworks published around 2018 and 2019, leading by FDA's publication of its RWE framework. Many additional countries, though, are still formalizing their drug approval process using RWE. Consequently, various guidelines regarding RWE and RWD for industries have been published. In Canada, for instance, several projects and initiatives have been hosted to examine the existing environment and infrastructure of RWD (Dai *et al.*, 2022; Government of Canada, 2018). The European Union has initiated the Data Analysis and Real-World Interrogation Network (DARWIN EU) project to collectively gather real-world evidence (European Medicines Agency EMA, 2021). China, on the other side, has also begun regional pilot applications of clinical RWD for drugs and devices in Hainan Province (CCFDIE, 2021)(Table 2).

Table 2. Regulatory Policies Updates

Country	Agency	Legislation	RWE Framework (Latest)	RWD Guidelines	Other Effort
US	FDA	21st Century Cures Act (2016)	FDA RWE framework (2018)	Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (draft guidance) (2023), Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products (2022) (Guidance for Industry Final)	FDA grants for 4 projects exploring the utility of RWE (2020) Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry (2021) (Draft) Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory

					Decision-Making for Drug and Biological Products (2021) (Draft Guidance for Industry) Data Standards for Drug and Biological Product Submissions Containing Real-World Data (2021) (Draft Guidance for Industry)
Canada	Health Canada	NA	The regulatory review of drugs and devices (R2D2) project (2021), Optimizing the use of RWE to inform regulatory decision-making (2019)	Elements of Real-World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle (2019)	Completed the project of Strengthening the use of real-world evidence and regulations for medical devices (2022)
China	National Medical Products Administration (NMPA)	NA	Guidelines for Real-World Evidence to Support Drug Development and Review (Interim) (2020)	Guidance for Real-World Data Used to Generate Real-World Evidence (Interim) (2021)	NMPA and Hainan Province jointly promoted the pilot application of clinical RWD of Drugs and Devices (2021) Technical Guidance for Real-World Study Supporting Research & Development and Evaluation of Pediatric Drugs (Interim)(2020)
Japan	Pharmaceutical and Medical Devices Agency	NA	Basic principles on the use of registries in approval applications (2021), Points to consider for ensuring reliability when registry data are used for approval applications (2021)	Points to consider for ensuring reliability when registry data are used for approval applications (2021) Utilization of Real-World Data - PMDA's approaches - (2021)	Established a RWD WG to deal with regulatory issues related to Real World Data such as using patient registry data and medical information databases. (2021) Posted a Q&A about Points to Consider for Ensuring the Reliability in Utilization of Data from Registry or Medical Information Database in Applications for Marketing Approval and Re-examination for Drugs (2022)
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)	NA	MHRA guideline on randomized controlled trials using real-world data to support regulatory decisions (2021), MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions (2021)	Points to consider for ensuring reliability when registry data are used for approval applications (2021) Utilization of Real-World Data - PMDA's approaches - (2021)	
EU	European Medicines Agency (EMA)	EU Pharmaceutical Strategy	EMA Regulatory Science to 2025 (2020), HMA/EMA EU Network Strategy to 2025 (2022)	EMA Patient Registry Initiative (2016–planned), and HMA/EMA Big Data Task Force data quality and representativeness framework (planned) Guideline on registry-based studies (2020)	Data Analysis and Real-World Interrogation Network (DARWIN EU) started working with hospital registries, and universities to collect real-world evidence. (2023)

4. ADDITIONAL CONSIDERATIONS

Another aspect of innovating in real-world evidence generation is by developing and employing digital health technologies. However, the use and interpretation of electronic health records (EHRs) data poses additional challenges that may arise out of potential biases imbedded in the original sources, records heterogeneity, and missing and/or non-standardized data formats. This notwithstanding, incorporating digital health data from wearable devices can provide more efficient access to care, and improve health literacy, adherence, and coordination. A recent advancement in this field comes from Germany's "Fast-Track" pathway, which established the market access for certain health applications known as DiGA, and passed through the regulatory process of the Federal Institute for Drugs and Medical Devices (BfArM) (Stern *et al.*, 2022). Currently, there are more than twenty approved digital applications under use for clinical practices, and BfArM promotes medical device development for more efficient patient care and clinical data collection (Stern *et al.*, 2022). Other countries, like the United States of America, are also making progress toward integrating regulated digital health applications. For example, "reSET", developed by Pear Therapeutics in Boston, MA (Stephanie Caccomo, 2017), received the first de-novo approval from the U.S. FDA as a digital therapeutic for examining product usage and efficacy through real-world data. Another example is "BlueStar", which focuses on diabetes and was developed by Welldoc in Columbia, MD, provides useful data collection with real-time feedback, drug usage guidance, treatment adherence promotion, and identification of clinical and non-clinical endpoints.

On the other hand, taking into consideration the recent and rapid progress of digital health initiatives, some concerns could be noted regarding the accuracy and reliability of collected data, along with the necessity of robust infrastructure and data management systems to handle the large amounts of data generated by digital devices. Further, there is still discussion about the optimal approach to managing and interpreting the implications of missing data (Stern *et al.*, 2022).

5. CONCLUSION

Upon analyzing targeted studies for specific diseases and worldwide regulatory developments, it is evident that all stakeholders encounter several common obstacles when utilizing RWE. These include challenges related to the quality and interoperability of RWD, as well as limited access to RWE (Schad and Thronicke, 2022). Methodologically, the main concerns center around the bias and confounding factors that may arise when employing RWE in experimental studies (Dai *et al.*, 2022). As such, randomized clinical trials (RCTs) are still the predominant type of study for generating reliable data used in drug approval processes.

Even though the current limitations of RWE outlined in this paper, there are multiple factors that point to its increased use. Aspects of the methodology that are driving RWE to become a major trend in the pharmaceutical industry include the growing digitalization of the healthcare industry, advancements in study designs, and the development of analytical methods that address statistical issues, alongside the growing support and promotion of the use of RWE by regulators worldwide. RWE has the potential to bridge the gap left by RCTs, particularly in addressing the limited number of patients in the rare disease market and promoting a fully representative patient population (Zura *et al.*, 2021).

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