Embracing the potential of real-world data: An industry perspective

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Abstract

Randomised controlled trials are the gold standard for evaluating the efficacy of medical interventions, offering robust evidence through controlled designs that minimise bias. However, their generalisability to diverse patient populations is typically limited. Real-world evidence (RWE), derived from real-world data, such as registries, electronic health records, claims databases, patient networks, social media, and wearables, has emerged as a vital complement to randomised controlled trials, addressing questions of effectiveness, safety, and cost-effectiveness across a medicinal product's lifecycle. In this article, we highlight the expanding role of RWE, from early development to post-launch activities, with examples from sponsor's RWE studies.

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Introduction

For more than five decades, randomised controlled trials (RCTs) have been the gold standard for demonstrating the therapeutic benefit of medical interventions prior to marketing authorisation.[1] By employing standardised methods to minimise bias, such as randomisation and blinding, while comprehensively measuring outcomes to establish efficacy of a novel product, the controlled design of RCTs provides significant advantages for evidence generation. On the other hand, RCTs are typically resource-intensive, time-consuming, and often conducted in relatively homogenous patient populations defined by restrictive inclusion and exclusion criteria. Therefore, the results of RCTs may not always be generalisable to broader, more diverse patient populations, which can leave certain questions about effectiveness and long-term safety of an investigational product unanswered.[2]

Real-world data (RWD) are used by regulatory authorities for post-marketing safety assessment and surveillance of medicinal products, as well as by payers and health technology assessment bodies to inform cost-effective coverage decisions. RWD refers to data collected outside of randomised clinical trials and encompasses information on patient health status and the delivery of healthcare from routine sources, such as data from registries, electronic health records, insurance claims, patient networks, social media, and patient-generated data from wearables. Recent advancements in computing technologies and the widespread availability of electronic health data have allowed RWD play an increasing role in drug development and healthcare decision-making across diverse stakeholders.

Real world evidence (RWE), in turn, is defined as clinical evidence derived from the analysis of RWD, for example, to characterise a population and disease and to evaluate the utilization, benefits, and risks associated with medicinal products.[3,4] RWE plays a pivotal role in addressing diverse needs across the product's lifecycle, from early development to post-launch activities (Figure 1). Historically, RWE has been primarily used to assess disease statistics and fulfil

post-authorisation safety monitoring obligations, but it has more recently taken on a strategic role in all phases of the product lifecycle, from early development to post-launch.

RWE in early and late drug development

Optimal planning of RWE begins early, with a forward-looking approach to anticipate future needs. During early development, evidence generation focuses on supporting decisions related to the positioning of investigational products and informing trial design and start-up activities. This includes characterising patient populations, understanding disease burden, and gathering insights into clinical practice (Figure 1).

For example, the European Scleroderma Trials and Research (EUSTAR) registry has been used to generate RWE on systemic sclerosis-associated interstitial lung disease (SSc-ILD). A prospective analysis of EUSTAR registry data on changes in lung function collected over 5 years from 800 patients identified risk factors for SSc-ILD and patterns of progression.[6] Also, a retrospective analysis of 6,000 patients in the EUSTAR registry used a stepwise cohort enrichment approach to identify patients with SSc-ILD at risk of disease progression and determine how many would be eligible for trial inclusion, with the aim of informing the selection of inclusion criteria and target populations for clinical trials.[7]

Similarly, claims databases have been used to generate RWE on unmet needs in generalised pustular psoriasis (GPP). A study in Japan compared profiles of patients with GPP and plaque psoriasis with the general population regarding comorbidities, medication use, health care resource utilisation, and health care costs in a 1-year follow-up period. The study highlighted that GPP patients had a higher disease burden, greater reliance on systemic treatments, and increased healthcare utilisation than those with plaque psoriasis.[8] A further study of claims data in the US highlighted the significant economic burden of GPP and palmoplantar pustulosis, including higher healthcare costs and more frequent inpatient visits than in the general population.[9]

RWE post-launch (growth and mature phase)

Post-launch, RWE generation focuses on the long-term effectiveness and safety in routine clinical practice to support clinical trial findings and payer discussions (Figure 1), as well as clinical adoption of a new product. Also, post-authorisation safety studies (PASS) may be needed to fulfil post-marketing commitments to regulatory authorities. Such studies are often conducted in non-interventional settings to complement efficacy and safety data available at the time of initial marketing authorisation.

An example PASS study evaluated the risk of acute pancreatitis in patients with type 2 diabetes treated with metformin and initiating empagliflozin therapy.[10] The study was conducted to address emerging safety concerns suggesting a link between several glucose lowering therapies, including sodium-glucose cotransporter-2 inhibitors, and this relatively rare but potentially serious and occasionally fatal condition.[11,12] In the study, data from two large US claims databases were used to compare the incidence of acute pancreatitis between patients prescribed empagliflozin and those prescribed sulfonylurea. The results supported existing evidence that the use of empagliflozin in patients with type 2 diabetes is not associated with increased risk of acute pancreatitis.

RWE might also be needed to support

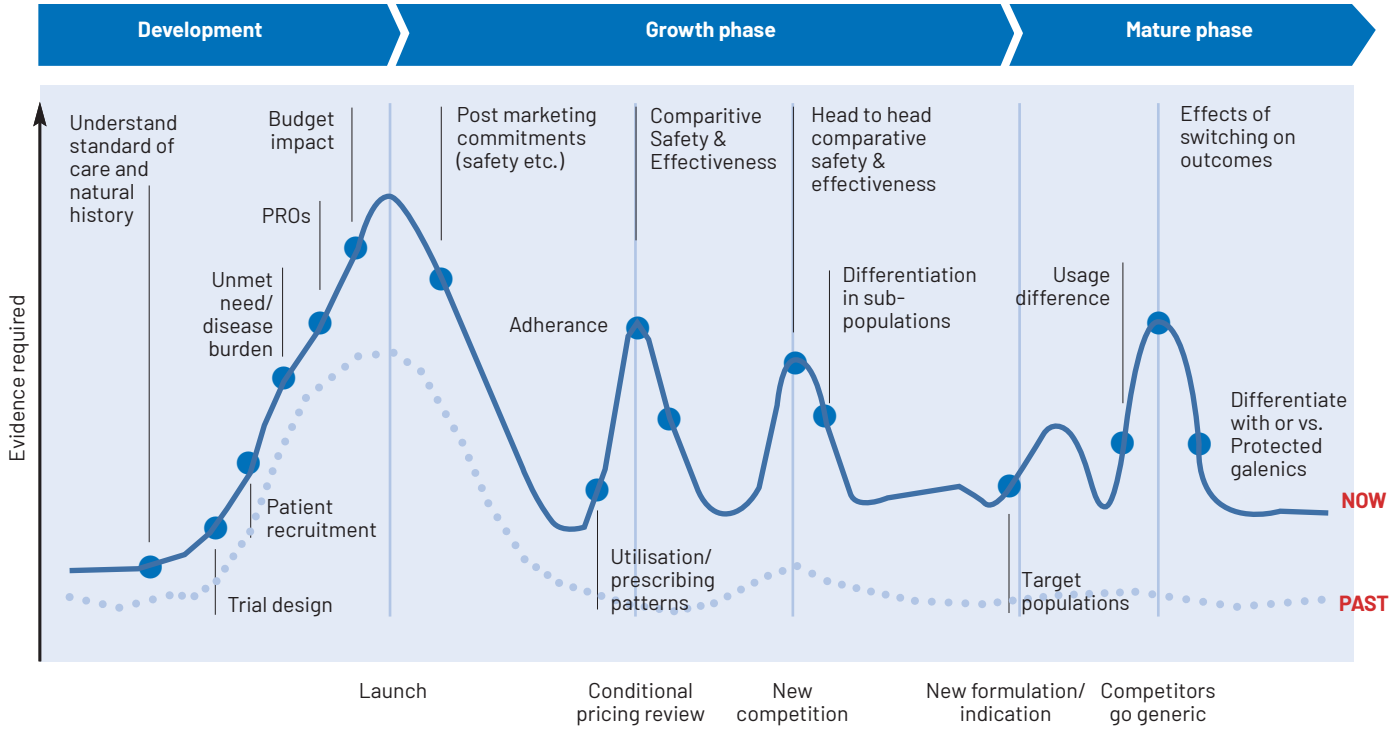

Figure 1. Real-world evidence generation along the lifecycle of a medicine. Adapted from Cerreta.[5]

Image: Freepik

different post-launch activities, such as pricing discussions, development of treatment guidelines, and clinical adoption.[13] In the mature phase of a medicine lifecycle, RWE helps address the impact of switching to generics on therapy outcomes and the preferences of patients (Figure 1).

The EMPRISE programme of studies: an example of RWE for bridging clinical trial findings with real-world practice

EMPA-REG OUTCOME, a prospective, placebo-controlled clinical trial, showed that patients with type 2 diabetes and established cardiovascular disease treated with empagliflozin had lower relative risks of cardiovascular death, all-cause mortality, and hospitalisation for heart failure.[15] Based on this trial, the US FDA expanded the indication for empagliflozin to reducing the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease.[16] This was followed by respective changes in major clinical guidelines on diabetes treatment for patients with cardiovascular disease.[17,18]

Following the EMPA-REG OUTCOME trial, the EMPRISE (EMPagliflozin compaRative effectIveness and SafEty) program was initiated to assess the real-world impact of empagliflozin in patients with type 2 diabetes. This is a global, multi-year monitoring programme with a new-user, active-comparator cohort study design in which 1:1 propensity score-matching between patients initiating empagliflozin or a comparator was launched to evaluate the effectiveness, safety, and healthcare utilisation of empagliflozin in routine care across a broad spectrum of baseline cardiovascular risk.[14] Using data from the US, Europe, and Asia, the EMPRISE programme confirmed that, in a broader population than in the EMPA-REG OUTCOME trial, the risk of cardiovascular events, hospitalisations for heart failure, and mortality are lower in patients treated with empagliflozin than in those treated with a dipeptidyl peptidase-4 inhibitor (DPP-4i) or glucagon-like peptide-1 (GLP-1) receptor agonist.

Final analysis of the EMPRISE US study, which included over 115,000 matched pairs of patients initiating empagliflozin or a DPP-4i, further demonstrated that the risks of several cardiovascular outcomes, including myocardial infarction or stroke, hospitalisation for heart failure, major adverse cardiovascular events, and cardiovascular and all-cause mortality were lower in patients treated with empagliflozin.[19] The study also showed that the risk of diabetic ketoacidosis was higher and the risks of acute kidney injury, severe hypoglycaemia, and retinopathy progression were lower in patients initiating empagliflozin than in those initiating a DPP-4i.

Subgroup analysis in the EMPRISE US study further revealed benefits in subgroups of patients, such as older patients and those with a history of atherosclerotic cardiovascular disease or heart failure, adding to the evidence generated in the EMPA-REG OUTCOMES trial.[19] Finally, the EMPRISE Europe and Asia studies, which encompassed over 85,000 matched pairs of patients across 11 countries, validated the findings of the EMPRISE US study in international settings.[20] Thus, RWE generated by the EMPRISE programme complemented the results of RCTs by adding insights on the effectiveness of empagliflozin in patients with type 2 diabetes with or without of a history of cardiovascular disease or heart failure across diverse routine care models.

In addition to providing insight on the effectiveness of empagliflozin in patients with type 2 diabetes, EMPRISE enabled a direct comparison of the cardiovascular effects of empagliflozin and GLP-1 receptor antagonists that have demonstrated a cardioprotective

potential in clinical trials. EMPRISE showed that empagliflozin was associated with similar risks of myocardial infarction or stroke and lower risks of hospitalizations for heart failure and cardiovascular mortality than GLP-1 receptor antagonists.[21]

Furthermore, the EMPRISE programme also allowed cost-effectiveness and healthcare resource utilisation to be assessed. The EMPRISE US study showed that, in routine clinical practice, health care utilization and costs of care were lower in patients initiating empagliflozin than in those initiating a DPP-4i, irrespective of the underlying cardiovascular disease.[22] Analysis of EMPRISE data in Sweden also demonstrated that empagliflozin reduced the rates of hospitalisation and in- and outpatient visits in patients with type 2 diabetes.[23]

Real-world studies on tiotropium/olodaterol in chronic obstructive pulmonary disease: another example of RWE for bridging clinical trial findings with real-world practice

Real-world studies on tiotropium/olodaterol in patients with chronic obstructive pulmonary disease (COPD) also illustrate how RWE can be used post-launch. Using US healthcare claims and commercial laboratory data, Quint et al.[24] compared the real-world effectiveness and safety of two combination maintenance therapies for patients with COPD, tiotropium/olodaterol and long-acting β_2-agonists (LABA)/inhaled corticosteroids (ICS). The study showed that the risks of COPD exacerbations, pneumonia, and treatment escalation to triple therapy were lowered more by tiotropium/olodaterol than by LABA/ICS, highlighting the importance of tiotropium/olodaterol in avoiding ICS overuse and reducing the risk of exacerbations in patients with COPD.

Further post-launch RWE on tiotropium/olodaterol was generated in two studies evaluating treatment patterns in COPD using US and UK healthcare databases.[25,26] The studies showed that, despite existing guidelines recommending ICS only for patients with severe COPD meeting certain criteria, ICS are overprescribed in both the US and the UK, potentially putting patients at risk of side effects and increasing unnecessary healthcare costs.

Conclusion

RWE has become an essential component of evidence generation across the medicinal product lifecycle. RWE enhances understanding of patient populations, disease burden, and clinical practice, and it provides evidence to inform trial design and optimise positioning of medicines. Post-launch, RWE further encompasses evaluation of real-world effectiveness, safety, and cost-effectiveness, complementing findings from RCTs. By providing insights into cost-effectiveness and healthcare resource utilisation, RWE enhances understanding of a medicine's value, supporting discussions with payers and informing treatment planning from a pharmacoeconomic perspective.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

Disclosures and conflicts of interest

AW and WP-R are employees of Boehringer Ingelheim Pharma GmbH & Co. KG. AD-L is an employee of Boehringer Ingelheim International GmbH.

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