Expanding the safety horizon: How real-world evidence shapes drug safety

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Abstract

Real-world evidence (RWE), generated from real-world data (RWD), is pivotal in evaluating the safety and effectiveness of medical treatments beyond the controlled settings of clinical trials. Unlike randomised controlled trials (RCTs), which often involve homogeneous patient populations and limited follow-up periods, RWD utilises diverse data sources, such as electronic health records, insurance claims, and patient registries, to assess safety and treatment outcomes in the general population. Safety data derived from RWD are critical for post-market surveillance, long-term safety monitoring, and the identification of rare or delayed adverse events. Furthermore, RWE provides insights into drug interactions and treatment effectiveness across varied demographic groups, including those underrepresented in clinical trials. Despite challenges related to data quality, confounding variables, and causal inference, RWE plays a crucial role in ensuring continuous safety monitoring and informing regulatory decisions post-approval.

In the continually advancing field of medicine, ensuring the safety and effectiveness of treatments remains a (or more likely *the*) primary concern. Clinical trials have long been regarded as the gold standard for assessing the safety and efficacy of novel treatments. These controlled research trials offer valuable insights into a drug's performance under precisely defined conditions. However, despite their critical role, clinical trials often fail to capture the full range of risks and benefits encountered in real-world practice, and are often restricted to a select patient population under controlled conditions. Real-world data (RWD), in contrast, derives information from routine clinical practice, offering a more extensive and representative perspective on a drug's safety and performance. RWD has become increasingly vital for monitoring the safety of medical interventions including pharmaceutical treatments once they are approved and used in broader populations.[1–3]

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What Is real-world evidence?

Real-world evidence (RWE) is based on RWD, which includes patient health information and healthcare delivery data routinely collected from a variety of sources such as electronic health records (EHRs), insurance claims data, patient registries, mobile health applications, and wearable devices.[2] RWE utilises these data to assess how a treatment performs in the patient population at large, as opposed to the often highly selective cohort involved in randomised controlled trials (RCTs). RWE also provides epidemiological information about adverse events, atypical treatment reactions and constitutes the basis for safety signalling.

Typically, RWD are observational, meaning they do not involve experimental interventions. Instead, they analyse the health outcomes of patients treated with a particular drug or intervention under standard clinical conditions. This methodology helps uncover valuable information about the treatment, including long-term effects, benefits, and potential risks.[3]

The role of safety data in real-world evidence

The role of safety data within RWE is particularly significant, as it provides a more diverse and comprehensive dataset compared with traditional clinical trials. The importance of safety data in RWE is evident in several key areas:

Post-market surveillance

Once a drug or device is approved by regulatory authorities, continuous monitoring of its safety and effectiveness in real-world conditions is necessary. RWE, drawing on data from a broader and more varied population, can identify adverse events or rare side effects that may not have been detected during the clinical trial phase.[4] (Figure 1) Additionally, real-world safety data can uncover potential drug–drug interactions

Image: Freepik

that were not identified in controlled clinical trial settings.

Post-market surveillance is crucial once a drug is approved and enters the market. RWD provides an effective mechanism for ongoing surveillance, allowing healthcare providers, patients, and regulatory authorities, to track adverse events and safety signals as they arise.[5] Without continuous monitoring, safety concerns may not be detected until they affect a large number of patients. In the past, several drugs have been withdrawn from the market after post-marketing surveillance revealed previously unrecognised risks. RWE serves as an ongoing safeguard, allowing regulatory bodies to take timely action when new safety issues emerge.[6]

Currently, EU drug regulations can require the collection of RWD as a condition for marketing authorisation. Such safety data collection is carried out through non-interventional post-authorisation safety studies (PASS). Even when not mandatory, PASS may be recommended to pharmaceutical companies, and they can then decide whether to conduct them. The design of PASS should be carefully considered and discussed with regulatory authorities. Often, these studies not only collect general safety information but also focus on specific abnormalities or suspected adverse drug reactions identified in RCTs, e.g. liver function abnormalities, QT prolongation, or tumour growth.

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It is worth noting that the EMA maintains the HMA–EMA Catalogue of RWD (formerly known as the EU PAS Register), which is a unique online source of RWD and RWE. As of May 2025, the catalogue includes 246 data sources and 3,067 studies.

Long-term safety monitoring

Clinical trials generally track patients for a limited period, often ranging from a few months to a few years. However, the full spectrum of a medication's long-term effects may not become apparent until later, sometimes much later. By following patients over extended periods, RWD can identify chronic side effects or benefits that only manifest with prolonged use. Longitudinal data particularly critical for drugs intended for long-term use, such as those used to treat chronic conditions like diabetes or cardiovascular diseases.[7] PASS, as discussed in the previous section, can serve as valuable sources for publications that provide insights into the long-term safety of new medicines. One example of such a study is ACROSTUDY, a global non-interventional safety surveillance study examining the long-term treatment of acromegaly with pegvisomant, a growth hormone (GH) receptor antagonist. Based on clinical trial data, concerns were raised about potential liver function abnormalities and pituitary tumour growth. As a result, marketing authorisation was granted on the condition that PASS be conducted, which subsequently generated reassuring safety data.[8]

Diverse patient populations

Clinical trials often impose strict inclusion and exclusion criteria, resulting in a homogeneous trial population. Consequently, the findings from clinical trials may not be fully representative of how a drug performs across different demographic groups, including patients of various ages, ethnicities, or those with multiple underlying health conditions. RWE trials can include diverse populations, thereby providing a more accurate depiction of how a drug affects different segments of the population. This is especially important when assessing safety for vulnerable groups, including the elderly, pregnant women, and individuals with comorbidities.[9] An example of such data is work performed by Vila et al who studied the treatment outcomes and safety of GH replacement during pregnancy in women with GH deficiency (GHD). The Pfizer International Metabolic Database (KIMS) collected RWD in adult patients with hypopituitarism, and 201 pregnancies were identified. Based on these data, the authors concluded that there was no relationship between pregnancy and GH replacement.[10]

Another example is a mortality study conducted using RWD from the same registry. The question of whether GH replacement therapy improves life expectancy in patients with GHD had remained unanswered for a long time. Gaillard et al. published RWE on mortality in patients with various underlying causes of GHD. Their findings showed that patients with hypopituitarism due to craniopharyngioma or aggressive tumours continued to exhibit increased mortality rates, while those with other underlying causes had life expectancies comparable to the general population.[11]

A different approach to studying mortality in a specific patient group was taken by Shankar et al., who investigated patients with drug-resistant epilepsy (DRE) using data from the Clinical Practice Research Datalink (CPRD).[12] CPRD is a real-world research database that collects de-identified primary care data from a network of general practices across the UK. Since DRE is not coded as a distinct diagnosis in the database, the authors defined specific criteria to identify this patient cohort. Based on this methodology, they were able to assess the prevalence of co-morbidities, as well as all-cause and epilepsy-related mortality, between January 1, 2011 and March 31, 2021. Their findings showed that the mortality rate in patients with DRE was approximately four times higher than that of the general population in the UK.

Improved understanding of drug interactions

Clinical trials typically involve a narrow patient population that meets specific inclusion criteria, leading to a homogeneous sample. As a result, the findings from clinical trials may not be fully generalisable to the broader, more diverse

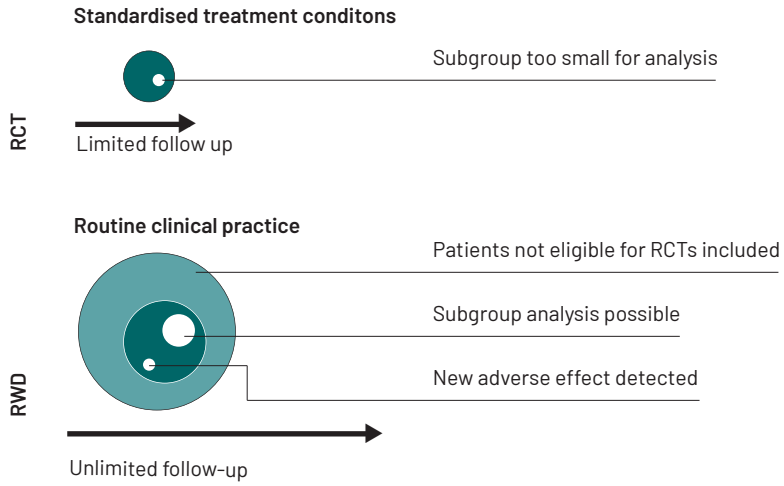

Figure 1. Sources of safety information

Abbreviations: RCT, randomised clinicial trial; RWD, real-world data.

Difference between RCT and RWD, courtesy of the late Dr Berhard Saller.

population. For example, a medication that shows efficacy in young, healthy participants in clinical trials may exhibit a different safety profile when used by older individuals or patients with multiple comorbidities.[13] RWE can reveal how demographic and health factors influence the safety and effectiveness of treatments in real-world populations.

Detection of rare and long-term adverse events

Certain adverse events are infrequent and may not be detectable in the relatively small sample sizes of clinical trials. (Figure 1) By utilising large, real-world datasets, RWE trials can identify rare but potentially serious side effects that may not have been apparent in the clinical trial phase. For instance, some adverse reactions such as specific cancers or severe allergic responses may only occur in a small subset of patients but could have significant health implications if not identified and addressed in a timely manner.[14] For example, meta-analyses found that insulin therapy seemingly has an association with increased overall cancer risk, and has significant associations with colorectal and pancreatic cancers.[15–17]

Although clinical trials are effective at detecting common side effects, they often lack the statistical power to identify rare or infrequent adverse events. RWD, which involve larger and more heterogeneous patient populations, are better equipped to detect these rare occurrences. For example, severe allergic reactions may affect only a small subset of patients in clinical trials, but these adverse events may become more apparent as the drug is used by a larger and more diverse population. Furthermore, certain safety issues – such as organ toxicity or cardiovascular complications – may not emerge until years after the initiation of treatment. RWD provide the longitudinal data necessary to monitor these long-term effects, thus offering a more complete picture of a drug's safety profile.[18]

Regulatory bodies and safety data

Regulatory agencies such as the EMA and the FDA acknowledge the growing importance of RWE in post-market surveillance. Both agencies are increasingly relying on RWE to monitor the safety of drugs and medical devices once they are available to the public. For example, the FDA has established guidelines for using RWE to support the approval of new indications for drugs and to assess ongoing safety.[19,20]

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The collection of safety data through RWE also enables reglatory authorities to act swiftly if new safety concerns arise. Should a concerning trend, such as a rise in adverse event reports, be identified, regulatory agencies can take timely action, including issuing warnings, modifying labelling, or even withdrawing a product from the market.[21]

Finally, speaking of long-term registries, it is impossible to omit the pioneering RWD registry run between 1987 and 2012; this was initiated at the request of regulatory authorities as a post-marketing surveillance study to follow 500 patients treated with GH (Genotropin®) for 5 years. It has evolved to be one of if not the largest and longest-running pharmaco-epidemiological study with four primary objectives:

1. to evaluate the long-term safety of GH and GH treatment outcomes in subjects who were treated with Genotropin®;
2. to determine relationships between clinical status, dosage schedule, and response to Genotropin® treatment;
3. to develop clinical tools for individualised GH treatment of children;
4. to contribute to the knowledge of growth and growth disorders.

It was a unique source of knowledge that was shared within the public domain and yielded 129 publications, cited in PubMed.[22]

Conclusion

RWD and corresponding RWE serve as a critical supplement to traditional clinical trials, providing valuable insights into the safety and effectiveness of treatments within diverse, real-world populations. By continuously monitoring safety data and identifying potential risks, RWE ensures that medical treatments continue to benefit patients well beyond the initial approval phase. As healthcare systems globally integrate RWD, the role of safety monitoring and post-market surveillance will continue to expand, ultimately ensuring that patients receive the safest and most effective treatments available.[23]

The examples presented in this article highlight the undeniable value of RWE in enhancing our understanding of complex medical conditions, guiding optimal therapeutic approaches, and improving everyday clinical practice.

Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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