REAL-WORLD EVIDENCE IN CLINICAL RESEARCH: CHALLENGES AND OPPORTUNITIES

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PRINEOS srl is a new strategic consulting company born and raised by passion, leveraging on a team with more than 25 years of expertise in the Life Sciences. Our goal is to improve and innovate Clinical Research in Healthcare providing services on: Biostatistics, Medical Affairs, Regulatory and Legal Affairs.

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INTRODUCTION

Randomized controlled trials (RCTs) are considered the scientific gold standard for demonstrating safety and efficacy of an investigational treatment, as well as obtaining its regulatory approval and authorization for marketing. However, the RCT paradigm is neither perfect nor infallible (1, 2).

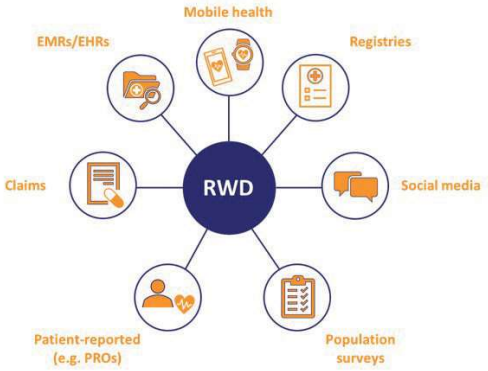
One pitfall of RCTs is that the study population does often not reflect the broader population managed in routine clinical practice, i.e. the real-world setting. Indeed, participants to RCTs are usually less clinically complex (e.g. they tend to be younger, healthier and on treatment with fewer drugs), and their number and the study duration are very limited (3, 4).

In light of the need to generate evidence in a real-world setting to inform healthcare decisions, with the ultimate goal to improve the efficiency of clinical research, the Real-World Evidence (RWE) i.e. the evidence generated through the analysis of Real-World Data (RWD), has assumed increasingly greater importance over time. It is increasingly recognized that RWE allows to bridge gaps in information that cannot be met by RCTs alone. Moreover, recent advances in digital and advanced analytics allow RWE to be implemented in novel manners (4, 5).

WHAT ARE RWD AND RWE?

RWD is defined by the European Medicines Agency (EMA) as "routinely collected data relating to a patient's health status or the delivery of healthcare from a variety of sources other than traditional clinical trials" (6).

The optimal RWD source depends on RWE hypothesis and purpose (7). These sources include electronic medical and health records (EMRs/EHRs), patient/disease registries, insurance and administrative healthcare claims (e.g. pharmacy data), primary and secondary patient-level data e.g. patient-reported outcomes (PROs), and population surveys, as well as emerging sources, such as data collected via mobile and wearable devices ar social media (1, 4, 8).



As defined by the Food and Drug Administration (FDA), RWE is "the clinical evidence regarding the usage and potential benefits 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 observational studies (prospectiv or retrospective) and pragmatic trials (i.e. simple trials involving prospective, randomized designs but with larger and more diverse patient populations than conventional RCTs) (8).

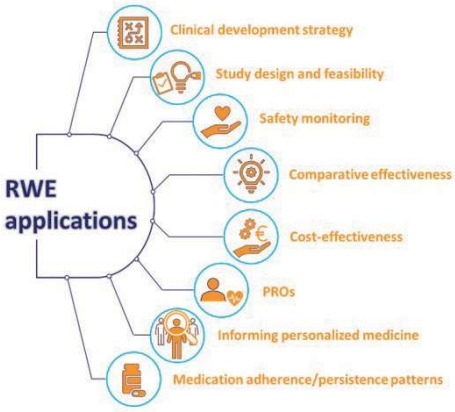
RWE APPLICATIONS

RWE from observational studies has been widely accepted to support post-approval safety monitoring and to answer pharmacoeconomic questions. Conversely, RWE integration in early development or other phases of a drug life cycle to contribute to healthcare decisions around effectiveness is only recently starting to be accepted and fostered by regulators, payers (i.e. organizations that pay for the care services administered by healthcare providers), Health Technology Assessment (HTA) bodies (organizations that determine the value of a healthcare intervention at different points in its lifecycle and provide recommendations on its price or reimbursement) and other stakeholders worldwide (1, 9, 10).

In the pre-marketing setting, RWE can help inform **clinical development strategy** and **study design and feasibility** by providing information on unmet clinical needs, disease burden, and clinical predictions (e.g. the number of patients eligible for a novel treatment) (3, 4, 10, 11).

The main applications of RWE in the post-marketing regulatory setting are the following:

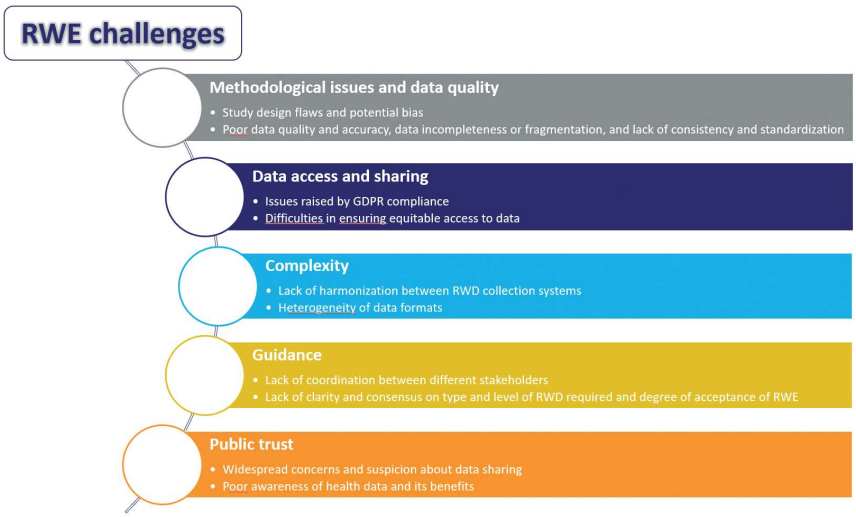
- **Safety monitoring.** Further information on safety signals or rare adverse events can be determined thanks to a larger number of patients and greater duration of drug use in a real-world setting (3, 5, 6, 10).
- **Comparative effectiveness.** RWE can uniquely provide insights into long-term, comparative effectiveness and tolerability from head-to-head comparisons with current standard(s) of care in routine clinical practice. Comparative effectiveness of a new intervention is increasingly valuable especially for reimbursement decisions and price negotiations (5, 10, 11).
- **Cost-effectiveness.** Payers and HTAs consider clinical and economic features of treatments equally important in coverage decision-making. RWE allows to evaluate the burden of treatment costs in relation to its benefits by providing information on healthcare resource utilization and costs (e.g. hospital readmission rates, disease-related costs, etc.) (5, 10, 11).
- **PROs.** Real-world PRO data (e.g. quality of life) offers the potential to capture patient's perspective during routine care. PRO importance has been increasingly recognized also in market access and reimbursement decisions (5, 6, 12).
- **Informing personalized medicine**. RWE can provide information on a drug benefit-risk profile for subgroups of patients who are generally excluded from RCTs, as well as help identifying the subsets of patients who can most benefit from a treatment. Moreover, RWE has the potential to support label expansion or new indications for an approved product (3, 5 ,6, 11).
- **Medication adherence and persistence patterns.** RWE allows to assess medication-taking behaviors, which is particularly relevant for patients suffering for chronic diseases, providing insights on patients' preference and characteristics associated with poor adherence/treatment discontinuation. Addressing these features could in turn help improve clinical outcomes and lower costs (5, 6, 11).



CHALLENGES TO RWE IMPLEMENTATION

The use of RWD has also its limitations, including but not limited to:

- **Methodological issues and data quality.** Study design flaws and potential bias (e.g. due to the lack of randomization) are of concern to various stakeholders. Moreover, RWE may be limited by poor data quality and accuracy, data incompleteness or fragmentation and lack of consistency, especially when particular sources of RWD are used, such as claims databases. At present, the large gap existing in data standardization, completeness and quality assurance is raising limitations in evidence derivation from RWD (1, 3, 6, 8, 10, 13).
- **Data access and sharing.** Data privacy legislations, especially the EU General Data Protection Regulation (GDPR), pose a major challenge to the collection and



analysis of RWD. Besides, diverging GDPR interpretations present at national levels in EU could impact cross-country data access and sharing, which is particularly important for rare diseases. Moreover, as RWD are generated from different sources, legal frameworks and governance arrangements for RWD access are needed to allow a more effective and equitable data access (3, 6, 10, 13).

- **Complexity.** The lack of harmonization between RWD collection systems, as well as the heterogeneity of data formats between different sources and countries are hindering RWE implementation (6,13).
- **Guidance.** The lack of coordination between different stakeholders on national and international levels regarding RWD translation into RWE is a major barrier to RWD collection and use. There is no overall clarity and consensus regarding the type and level of data required by different stakeholders. Besides, guidance provided by agencies often reflects the ideal end-stage for RWD, where data of enough quality are available in sufficient quantities. Moreover, the degree of acceptance to integrate RWE into regulatory decision making, especially before marketing, differs worldwide (1, 6, 8, 10, 11, 13).
- **Public trust**. Widespread concerns and suspicion within the general population about data sharing could hinder the adoption of RWE. It is crucial to raise public awareness of health data and its benefits, as well as involve patients in RWD collection (6, 13).

CONCLUSION

Although many questions and challenges remain, RWE is increasingly recognized as additional element to inform healthcare decisions in the context of market access, reimbursement decisions, price negotiation, and pharmacovigilance (4,10).

RWD and RWE are becoming parts of integrated evidence generation in the research and development process, especially in light of the changes linked to the advent of novel therapeutics (e.g. advanced therapy medicinal products) and the updated concept of "value" of a drug (1, 10, 11).

The hoped-for benefits of RWE is not only to improve research generalizability, but also to expand the available evidence for patients with greater disease severity and/or heterogeneity, and multi-morbidity than typically would be feasible in RCTs (14).

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