# Real-world data: bridging the gap between clinical trials and practice

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## Summary

**Real-world data (RWD) are rapidly emerging sources of information for patients, clinicians and regulators. While randomized controlled trials (RCTs) reduce bias and confounding through the randomization process and provide the highest quality of evidence regarding drug efficacy, RCTs may be impractical or unfeasible for rare diseases or disease subsets. And yet, studies attempting to replicate clinical trial results using observational datasets have failed. Given the inherent differences between observational data and clinical trial results, this discordance is not surprising. However, RWD may still have independent value as complementary tools to trial results. In this viewpoint, we explore the challenges of RWD and discuss key questions that clinicians, patients, and regulators will need to consider when faced with positive efficacy data from clinical trials, and negative effectiveness data from real world studies. Finally, we explore novel trial designs that might help bridge the gap from RCTs to RWD.**



Keywords: Regulatory approval; Real-world data; Clinical trials

## Introduction

In oncology, real-world data (RWD) and real-world evidence (RWE) are rapidly emerging as common sources of information for patients, clinicians, and regulators. Although RWD and RWE have been used for years to support post-marketing approval and drug safety, the 21st Century Cures Act enacted into US legislature in December 2016 has led to an increase in the use of RWD and RWE for regulatory submissions. Between 2017 and 2019, only 13% (5/40) of evaluated oncology submission to the FDA included RWE to support efficacy,[1] compared to 70% (30/43) of submissions from 2019 to 2021 using RWD to support efficacy and/or safety.[2] The use of single-arm trials supplemented with external real-world comparators has also been used on occasion to support regulatory approval,[3] generally in the setting of rare diseases.

Both the European Medicines Agency (EMA)[4,5] and the Food and Drug Administration (FDA)[6] have released position papers outlining their support for RWD and RWE in regulatory submissions. The FDA defines RWD as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources", while RWE is defined as "evidence about the usage and potential benefits or risks ... derived from analysis of real-world data".[7] In other words, the FDA stipulates that clinical trials can also generate RWD if collected from administrative sources through data linkage. In contrast, the EMA defines real-world data 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", thereby restricting RWD to non-interventional studies. RWD sources include patient files, electronic records, routinely collected administrative data, registries, patient questionnaires, wearable device information, and social media, all with varying levels of population coverage and quality.

While RCTs are designed to answer the question "Can the drug work?" (i.e. efficacy), observational studies and RWD are more adept at answering the question "Does the drug work?" (i.e. effectiveness).[8,9] For most tumor types and treatments, surrogacy between efficacy and effectiveness is not established—in other words, even if a drug works in a clinical trial, it may not improve outcomes when delivered in the real world. This efficacy-effectiveness gap is widely recognised,[10] and informs daily discussions with patients. If RWD outcomes are not a valid surrogate for clinical trial outcomes,[11] can RWD play a separate role, using distinct endpoints to evaluate important questions and improve the time to drug access for patients? Can efficacy and effectiveness questions have independent value for clinicians, regulators, and patients, regardless of surrogacy? Finally, if a drug has demonstrated efficacy in

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clinical trials but cannot demonstrate effectiveness when adopted in a real-world population, does it still have value and should it still be prescribed? These questions require careful evaluation as the cancer community develops processes and pathways to integrate the growing amount of real-world data into regulatory, funding, and clinical decision making.

## Study designs and endpoints

From a methodological standpoint, RWD cannot compete with the quality of data generated by randomized controlled trials (RCTs). Through randomization and blinding, RCTs reduce bias and confounding, both known and unknown, providing the highest quality of evidence regarding drug efficacy. However, RCTs may be impractical or unfeasible for rare diseases or disease subsets, or due to costs, logistical challenges, and the long lag-time to obtaining results. This lag time for overall survival (OS) outcomes has been a principal argument behind the use of surrogate endpoints such as progression free survival (PFS) and disease-free survival (DFS). However, in reality the time lag for OS compared to PFS is likely much shorter than often assumed and has been estimated to be 11 months.[12] The stringent eligibility criteria and often limited geographical and socioeconomic diversity of most RCTs makes generalizing results difficult.

Evaluable endpoints may also differ between clinical trials and RWD. While some efficacy endpoints such as OS may have comparable definitions, PFS (defined as the time from drug initiation to tumor growth of >20% on serial imaging) is challenging to replicate and alternative efficacy endpoints such as time to treatment failure are often used as proxy. Quality of life and toxicity endpoints are also difficult to evaluate in administrative data sets, and proxy measures such as hospitalizations and emergency visits are sometime used. However, the growing use of wearable devices, health-related mobile applications and social media platforms are driving transformations in this field. Finally, cost-effectiveness analyses may differ between trials and real-world data,[13] due to differences in the intensity of follow-up, definitions of efficacy, and the time horizon for evaluation. These differences make it difficult to evaluate surrogacy between trial and real-world data.

## Surrogacy of RWD and clinical trial outcomes

Several studies have attempted to replicate clinical trial results using observational datasets. Kumar et al.[14] performed comparative effectiveness analyses to replicate results from 141 RCTs using observational data from the National Cancer Database, and found that discordance was frequently observed, in both the hazards ratio (HR) for OS and the associated p value. Similarly, Soni et al. replicated 121 clinical trials in oncology using a variety of observational data sources and found no correlation between the HR estimates in the observational and randomised studies. Given the inherent differences between observational data and clinical trial results, this discordance is not surprising. There is also significant variability in the quality and methods used in observational research which may influence the validity and reproducibility of results. As a result, the FDA is investing in efforts to replicate trial RCT results using more rigorously designed observational studies, and exploring ways to integrate RWD acquisition into traditional and pragmatic trial designs.[7] Observational research requires distinct but equally rigorous quality and methodological approaches, and emphasis should be placed on transparency and reporting in accordance with guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the International Society for Pharmacoepidemiology (ISPE),[15,16] and the STROBE guidelines for observational data.[17]

Even if there is no proven surrogacy between RWD endpoints and clinical trial endpoints, high quality RWD/RWE examining the question "Does the drug work?" may still have independent value as complementary tool to trial results. Observational studies can answer additional important complementary questions regarding the real-world effectiveness, toxicity and cost-effectiveness of drugs among representative populations, and can explore effectiveness in populations not well represented in clinical trials. As an example, Palbociclib was initially approved for use in women with advanced breast cancer based on the PALOMA-2 and PALOMA-3 trials. In 2019, the FDA expanded the indication for use to include men based in part on real-world effectiveness and safety data from electronic health records and insurance claims, and data from two phase I studies.[18] RWD also offer advantages in terms of cost,[19] the size and scale of data coverage, the timeline to analysis, and can explore questions regarding real-world access and equity. However, RWDs cannot, and should not, replace RCTs as the gold standard for determining whether a drug can work. Promoting observational studies from routine practice as alternative data sources to demonstrate efficacy and support regulatory approval in the absence of proven surrogacy between these measures could lead to harmful conclusions.[20]

## Positive efficacy, negative effectiveness– what to do next?

As RWD continues to emerge as a common source of data, stakeholders (including patients, clinicians, regulators and funding agencies) will face a growing number of scenarios where trials demonstrate positive results, but these do not translate into routine practice. This may prompt important questions from patients such as "If the drug hasn't been shown to benefit patients in the

real world should I still take it?" Clinicians will be faced with increasingly complex discussions as we try and explain the differences between trial and real-world populations, and as we try and analyse reasons for these discordant results. Should such discordant results force clinicians to adhere more rigorously to prescribing the drug only to patients who meet the clinical trial criteria? And what answers can we offer to patients who fall outside of these eligibility criteria? Regulatory bodies may be faced with similarly challenging questions, such as "should drugs that fail to demonstrate population-level benefit in the real-world still be approved?", and "Should a demonstration of real-world benefit be required as part of drug's regulatory lifecycle?" Funding agencies will also face questions, such as "If a drug is cost-effective based on clinical trial analyses, but is not cost-effective using real-world data, should it still be funded?", and "Should drug pricing be informed by real-world effectiveness?" These questions require careful consideration as we increasingly rely on real-world data for treatment, regulatory and funding decisions.

## Novel study designs that may bridge RWD and clinical trials

Given the limitations of both RCTs and observational RWD, hybrid and alternative study designs[21] capable of generating RWE may help bridge the gap between clinical trials and RWD. As an example, pragmatic trials offer unique opportunities to adopt the methodological rigour of the RCT with the potential cost savings and practical advantages of real-world studies.[22] Pragmatic clinical trials must have 3 key attributes: (1) an intent to inform decision makers (patients, clinicians, administrators and policy makers); (2) an intent to enroll a population relevant to the decision in practice or representative of the patients or populations and clinical settings for whom the treatment is relevant; (3) and an intent to streamline procedures and data collection, so that sufficient power can be allocated towards informing clinical and policy decisions.[23] Depending on the design, pragmatic trials may generate randomized evidence within the context of a real-world population. Hybrid trials, which use the traditional clinical trial design but incorporate pragmatic trial elements, also have the capability of using RWD to generate RWE.

The FDA has launched Project Pragmatica to promote pragmatic trials capable of generating RWD and promoting trials designed with functional efficiencies, such as fewer eligibility criteria, increased trial flexibility, and enhanced patient centricity.[24] The European Organisation for Research and Treatment of Cancer (EORTC) has also voiced support for select RWD studies, prioritizing the execution of clinical trials that produce randomized real-world evidence,[25] of which pragmatic clinical trials are an example. Other examples of collaborative efforts to increase pragmatic trials include the REACTs collaborative[26] designed to compare standard approved treatments in a real-world setting across a broad range of patients, and NIH Pragmatic trials Collaboratory designed to strengthen the national capacity to implement large-scale research studies that engage health care delivery organizations as research partners.[27]

## Conclusion

Interest in using RWD to support regulatory submissions is growing. However, we believe that the prerequisite for most approvals should still remain robust evidence regarding efficacy based on a well conducted RCT designed to meet a clinically meaningful endpoint for patients. Observational and RWD cannot answer the question "Can a drug work?" and treating patients before efficacy has been clearly demonstrate places patients at risk of harm and toxicity without proven benefit. However, there may still be value in prospective observational studies evaluating "Does the drug work" in real world practice, though many questions remain regarding how patients, clinicians, regulators, and funding agencies should use the results when there is a lack of effectiveness despite proven efficacy.

### Contributors

BEW and CMB both contributed to the idea, writing and editing of this manuscript.

### Declaration of interests

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