Fortrea

The power of real-world data in clinical development and post-market activities

Today's clinical trials need to align with the evidence requirements of regulators, payers, physicians and patients, ensuring that trial outcomes are relevant for decision-making on benefits, risks and value considerations. Given that the use of real-world data (RWD) and real-world evidence (RWE) is increasingly of interest globally to regulators and other decision-makers, this white paper provides an overview of RWD and RWE, discusses its benefits in drug development and post-market activities and shares examples of how RWD/RWE supports a product's value throughout the development life cycle.

The U.S. Food and Drug Administration (FDA) defines RWD as data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources, outside of traditional clinical trials. RWE is the clinical evidence about the usage and potential benefits or risks of a medical product or intervention derived from analysis of RWD.

Rising interest in RWD and RWE

Regulators, payers, physicians and others are interested in relying on RWD and RWE to support their decision-making processes. Specifically:

- **Regulators** are seeking to leverage RWE as the basis for natural history of disease studies, epidemiological benchmarking, diversity action planning, external control arms and pragmatic and adaptive trial designs
- **Payers** are requesting RWE to support burden of illness baseline analysis as well as product value claims regarding comparative and cost-effectiveness research

Regulatory bodies are increasingly highlighting the importance of RWE. For example, the European Medicines Agency (EMA) alongside the European Medicines Regulatory Network (EMRN) is working toward better integration of RWD and RWE alongside the gold standard of randomized controlled trials into regulatory decisions on the development, authorization and supervision of medicines.[1] RWE provides patient-centric data that traditional routes may miss, such as comparative effectiveness evidence across diverse sub-populations of patients. RWE is especially valuable for orphan drugs and rare diseases as it can inform benefit/risk assessments and support market access for products that reach limited patient populations in traditional clinical trials.

- **Physicians** take an evidentiary approach to prescribing, considering a rapidly expanding evidence base inclusive of clinical trial data and real-world data derived from electronic health records (EHR), registries, claims databases and patient-generated health data (PGHD) from digital health technology such as wearables and sensors
- **Patients** are becoming more consumer-centric in healthcare and expect personalized engagement in clinical research. Data on their lived experiences fills gaps in RWD by offering a full picture of their health status. PGHD allows stakeholders to understand the state and trajectory of a disease or health state, enabling personalized study and care programs to drive drug development at scale
- **Improved collaboration** between patients, regulators, physicians and payers is leading to more streamlined, efficient and innovative trial designs. This collaboration not only helps reduce costs and delays but also creates shared value in clinical research across stakeholders

Understanding the benefits of RWD and RWE in drug development and post-market activities

RWD sources include traditional types of records like EHRs, pharmacy and medical claims databases, laboratory and imaging data and patient registries. Other real-world data is also available, derived from digital sensors, wearables and the Internet of Medical Things (IoMT) as well as data on social determinants of health (SDOH). Tokenization enables the linkage of traditional EHR and claims records to these emerging data sources, creating broader and deeper pools of data that can play a crucial role in enhancing trial design, efficiency and outcomes. RWD and RWE can offer:

1. **Optimized approval timelines:** Leveraging RWD allows for faster decision-making by regulators and brings new life-changing treatments to patients in need.[2] For instance, the FDA approved Pfizer's IBRANCE® (palbociclib) for male breast cancer based on RWE, including EHR and post-marketing data. Enriching clinical trial design with RWD on patient phenotype, genotype, healthcare resource utilization (HCRU), laboratory and diagnostic data, PGHD and SDOH improves the specificity of inclusion and exclusion criteria. Adaptive clinical trial design can also accelerate regulatory approval, which can precipitate a need to validate safety and efficacy data with RWE supporting the benefit-risk profile of the innovative therapy.[3]

2 **Cost savings:** RWD can improve the efficiency and effectiveness of clinical trial operations at multiple stages of the process:[2]

Clinical trial planning, feasibility and optimization: RWD allows in-depth exploration of the target patient population (TPP),[4] allowing sponsors to gain insight into real-world populations, which informs hypotheses, feasibility, potential eligibility and expected trial performance, including expected recruitment rate.[5]

Site selection and patient recruitment: RWD can improve the precision of site selection.[2] When anonymized patient-level data (APLD) is integrated with population-level data and these data insights are combined with operational intelligence, RWD enables a focus on target sites and locations, accelerates recruitment and improves retention of patients and site partners.[6]

RWD collection with digital technologies: Digital tools like wearable sensors and virtual assistants enable efficient data capture, timely data review and rapid communication, reducing trial costs and time and increasing data quality and integrity.

At the pre-award stage, Fortrea uses multiple RWD assets to identify and test assumptions. Fortrea is able to access multiple RWD assets, including Electronic Health Record (EHR), claims data, lab data, epidemiological data and reimbursement data in most regions across the world.

Fortrea's clients have direct access to our Fortrea Site Advisory board, which is representative of more than 440 sites across nine countries with experience across 25 therapeutic areas. The Fortrea Site Advisory Board informs us of the principal investigator (PI) perspective as well as that of other stakeholders in the clinical trial ecosystem, specifically providing early feedback into protocol strategies, which we augment with RWE to develop fit-for-purpose trial designs.

Recognizing that clinical trial models are evolving rapidly, we offer innovative approaches that increase patient recruitment, engagement and retention while promoting continuity for your clinical trials. Fortrea has a dedicated Digital Health and Innovation team that supports clinical trial/protocol design. This expert team offers digital and mobile health solutions and a host of remote, mobile and virtual capabilities, which sets a new standard for efficiency and streamlined and quality capture.

3 **Other benefits of RWE in trials:** RWD captures information from everyday patient care, providing insights beyond the controlled environment of clinical trials. This broader context helps improve the generalizability of trial results to real-world patient populations.

Patient-centered drug development: Applying RWD supports the development of patient-centric protocols. Fortrea seeks to understand patient preferences and values, and applies cutting-edge "systems thinking" and "human-centered design" methods to create a positive trial experience. Using RWD helps to tailor eligibility criteria, sub-population delineation, endpoints, study time horizons and other trial design elements to optimize patient centricity and improve operations and retention.

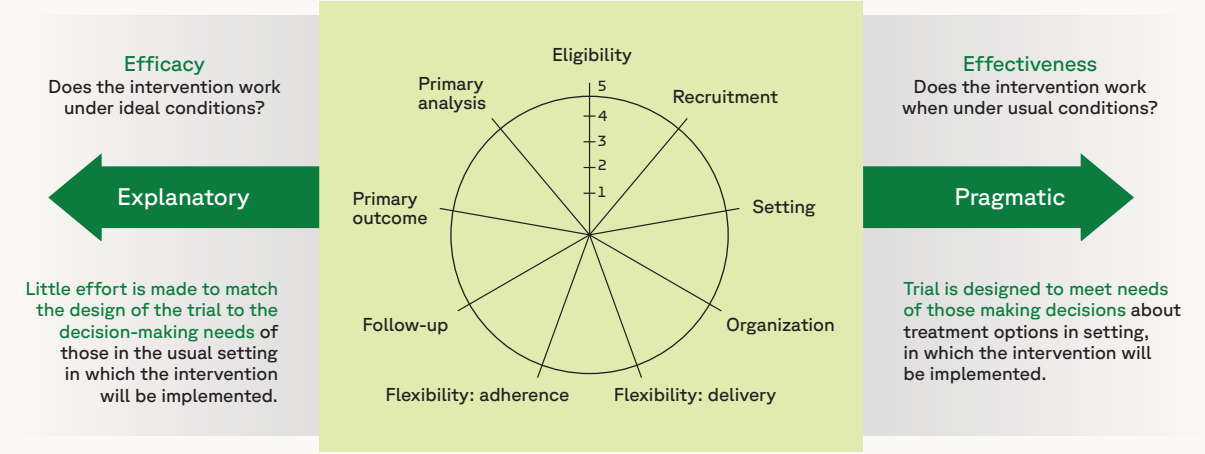
Patients' lived experiences fill gaps in RWD by offering a window into health status. Fortrea routinely accounts for the Voice of the Patient during clinical trial/protocol design and strategy considerations. We believe that patient insights are critical to drug development as they provide insight into the needs of the patient population from the patient perspective. Our Patient Intelligence platform gathers data from patients regarding their disease, satisfaction with their care and views on clinical trial participation. In addition, gaining a holistic understanding of the patient allows the study team to assess study eligibility, reducing screen failures and protocol deviations during operationalization of the study. Our patient insights program ensures robust and timely endpoint delivery mechanisms led by the patient and site voice.

Diversity in clinical trials: RWD analysis of claims and EHR helps us understand the epidemiology of disease and risk factor distribution across diverse populations in heterogeneous settings to set Diversity Action Plan (DAP) goals. Based on patient-level RWD analyses, sites are selected to achieve DAP goals and ultimately enhance trial populations such that they represent the intended treatment population. A draft guidance issued in June 2024 includes language requiring that DAPs be submitted in advance of Phase III protocol submission and RWE will play a key role in these submissions.

Pragmatism: Leveraging RWD allows for more pragmatic trial designs, reducing investigator workload and increasing the speed of evidence generation. Pragmatic trials yield findings that are more generalizable to real-world settings than trial results.

The Fortrea team deploys the PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary 2) framework (https://www.precis-2.org) when evaluating study design elements on a continuum of "explanatory to pragmatic" to ensure the optimal balance is struck to maximize effectiveness and efficiency of a study. See Figure 1 for a Pragmatic Clinical Trial framework from PRECIS-2.[7]

Figure 1. Pragmatic clinical trial design is on a spectrum



External control arm (ECA): The FDA has a long history of using RWE to monitor and evaluate the safety of approved therapies in the post-marketing environment, where it uses data from EHRs, for example, with the Sentinel System.[8] Real-world data can be used as an ECA for interpreting the long-term safety and efficacy results from single-arm trials.[9] The use of historical RWD, as a benchmark, can be particularly useful for characterizing the natural history of the disease, including treatment patterns and outcomes for a disease that is not only rare but also has insufficient data about its natural history (e.g., severe unmet need, scarcity of available patients).[10] This is particularly useful when there have been no noticeable shifts in the standard of care, medical practice, patient management or patient characteristics as the historical RWD provides insight into how the disease progresses under standard care.[11] However, this is different from that of an ECA that involves concurrent RWD to serve as the control arm of the trial.

4 Real-world evidence (RWE) generation

RWD enables real-world evidence development to complement and supplement randomized controlled trials (RCTs). RWD can be translated to RWE to provide insights into treatment effectiveness, safety and outcomes beyond controlled clinical trials. These data can provide a full picture of the patient experience and fill gaps in rare disease, oncology, personalized medicine, high patient comorbidities, long-term outcomes measurement (i.e., regulatory-mandated long-term follow-up for gene therapy) and other complex scientific areas of research.

Improved post-market surveillance: RWD enables continuous post-marketing surveillance (PMS), identifying potential adverse events or other outcomes in real-world settings. Identifying RWD sources and developing baseline assessments of patient risk factors, natural history of disease, standards of care and other observations of the current state informs future state PMS as well as generates RWE on outcomes and value demonstration.

CASE STUDY:

Utilizing retrospective data to meet post-marketing requirements

Applying a hybrid approach to a study accelerated approval by four years and saved our client $10 million

Objective: Fortrea (then operating as Covance) examined the incidence of adverse events (AEs) to address a sponsor's FDA post-marketing requirement. They examined the incidence of treatment-emergent adverse events (TEAEs) associated with SUPREP® and other common prescription bowel preparations in the three months following screening colonoscopy with a prescription for bowel preparation in the prior 60 days.

Methods: Using a hybrid approach, the team gathered medical and pharmacy claims, laboratory results and electronic medical records rather than purely prospective data collection. They utilized MarketScan® claims and GE electronic medical record (EMR) data and proposed to prospectively collect data from each data source until the required sample patient population was achieved. The unadjusted and adjusted cumulative incidences of AEs were estimated using Kaplan-Meier and Poisson regression, respectively.

Results: Based on the analysis, the rate of reported AEs was low. Patients using SUPREP were less likely to experience adverse events compared to patients using other products. The report generated by these data satisfied the FDA's post-marketing requirement, saving the client over four years and $10 million in costs. The work was published in a peer-reviewed journal, Digestive Diseases and Sciences.[12]

Disease burden estimates: RWE helps establish the clinical, economic, humanistic and social burden of a disease. For rare diseases, it raises awareness, estimates incidence/prevalence and characterizes affected populations.

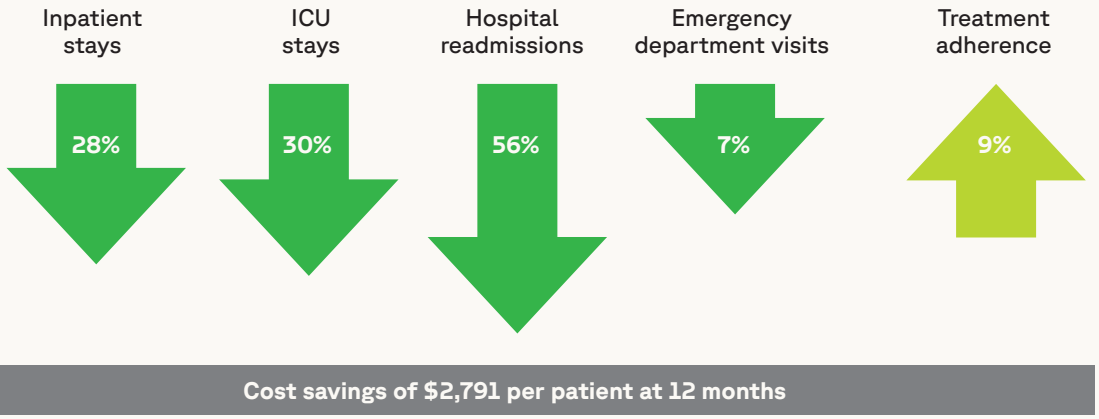
Fortrea supports our clients by communicating disease burden through peer-reviewed publications, global dossiers and interactive economic models.

Value demonstration: RWE contributes inputs for the development of value messages, economic models and value dossiers, helping justify resource allocation and adoption of new technologies by payers and health technology assessment agencies. Increasingly, public and private payers are demanding value-based pricing and innovative financing such as subscription models and warranties, which require RWE adjudication of patient outcomes.

With commercialization in mind, Fortrea acts as a development partner to our clients, which includes RWE generation strategies aiming to show product value before, throughout and after the development process. Figure 2 provides a recent case study where Fortrea demonstrated this concept.

Figure 2. Resource utilization in patients with opioid use disorder

Patients on a prescription digital therapeutic (PDT) had lower utilization and increased treatment adherence compared to controls.[13]



Evidence needs alignment: The Fortrea team takes an "integrated evidence planning" approach to clinical trial design, incorporating multiple stakeholder perspectives. RWD analysis provides insights into stakeholder risk factors, patient healthcare journeys and outcomes. Figure 3 summarizes the Fortrea method of generating RWE to support our client's product vision throughout the drug development life cycle.

Figure 3. Fortrea's 10-step RWE generation strategy

- Understand your product vision
  (unmet medical need, target audience, intended impact on healthcare)
- Generate research questions aiming to show product value compared to the current standard of care
- Identify relevant data sources
- Evaluate data accessibility and feasibility, and define data standards
- Evaluate innovative RWD collection technologies
- Plan data collection and analysis methods
- Collaborate with stakeholders
  (clinicians, researchers, patients, regulators, payers and data providers)
- Consider data validation and quality assurance
- Continuous monitoring and improvement throughout data collection
- Stay informed about evolving regulations and guidelines

Objective and subjective data: With the generation of RWE through the collection and analysis of physiological and psychological data, a complete picture of the patient is obtained and robust RWE is generated. This meets the needs of the regulators for approvals, the patient for increased quality of life and payers for medication provision and reimbursement.

Fortrea's Digital Health and Innovation team supports our clients during the clinical trial/protocol design stage to provide solutions when using eCOA and eDiaries to digitally capture data, improve quality and speed critical decision-making for sites and sponsors as well as support regulatory decision-making.

Support your product vision throughout the drug development lifecycle with RWD

Fortifying clinical development with RWD enhances study efficiency, patient relevance and regulatory/payer/prescriber decision-making, ultimately benefiting patient outcomes. Purposeful and systematic RWD application to clinical development design and operations can optimize regulatory approval timelines, reduce costs, enhance study generalizability and generate RWE of a favorable benefit-risk profile and value proposition.[5]

RWD effect	Application
Streamlined recruitment	RWD can help identify and recruit eligible participants more efficiently, enhance the diversity of participants and increase site centricity,[3] thus reducing the time and resources spent on recruitment.[14]
Earlier identification of effective interventions	By analyzing existing data, researchers can identify promising treatments earlier, potentially shortening the trial duration.[5]
Reduced need for new trials	Off-label use of older and less expensive treatments can often offer efficacy and safety similar to those of their on-label counterparts,[5] while in some cases, RWD can support regulatory decisions, such as expanded label use, without the need for new randomized clinical trials.[15]
Enhanced planning	Using RWD for planning eligibility criteria and other trial aspects can lead to more efficient and cost-effective trial designs.[4] Analyses of RWD can be used to assess the feasibility of pragmatic RWE trials before they are discussed with regulators.[5]
Long-term, post-trial outcomes	Identifying former study participants and tracking their outcomes from an efficacy and safety standpoint can facilitate a more complete understanding of important long-term outcomes.[5]
Trimming the trials: more efficient data collection	RWD may help reduce the complexity and costs of data collection process by informing trial designers as to what variables are most often used clinically, which variables are informative and which variables might be redundant.[5]

Fortrea sources broad and deep RWD to fortify the clinical development bridge from molecule to market, ensuring that we span evidence gaps for multiple stakeholders and accelerate affordable, equitable access to your medical innovation.

Learn more about our full range of CRO consulting services:
https://www.fortrea.com/solutions/fortrea-consulting-services.html

References

1. European Medicines Agency. Real-world evidence framework to support EU regulatory decision-making 2023. https://www.ema.europa.eu/system/files/documents/report/real-world-evidence-framework-support-eu-regulatory-decision-making-report-experience-gained_en.pdf. Accessed Sept. 23, 2024.
2. Berger, M, et al. A framework for regulatory use of real-world evidence. 2017. https://healthpolicy.duke.edu/sites/default/files/2020-08/rwe_white_paper_2017.09.06.pdf. Accessed September 18, 2024.
3. Pryluk, R. Adaptive trial designs will increase clinical trial speed, safety, and effectiveness. *STAT*. July 2024. https://www.statnews.com/2024/07/12/adaptive-trial-designs-increase-speed-safety-effectiveness/. Accessed Sept 30, 2024.
4. Dagenais S, Russo L, Madsen A, Webster J, Becnel L. Use of Real-World Evidence to Drive Drug Development Strategy and Inform Clinical Trial Design. *Clin Pharmacol Ther.* 2022 Jan;111(1):77-89. doi: 10.1002/cpt.2480.
5. Evans SR, Paraoan D, Perlmutter J, Raman SR, Sheehan JJ, Hallinan ZP. Real-World Data for Planning Eligibility Criteria and Enhancing Recruitment: Recommendations from the Clinical Trials Transformation Initiative. *Ther Innov Regul Sci.* 2021 May;55(3):545-552.
6. Rudrapatna VA, Butter AJ. Opportunities and challenges in using real-world data for health care. *J Clin Invest.* 2020 Feb;130(2):565–574.
7. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* 2015 May 8;350:h2147.
8. U.S. FDA. Framework for FDA's Real World Evidence Program. December 2018. Available at https://www.fda.gov/media/120060/download. Accessed August 20, 2024
9. Dreyer NA. Advancing a framework for regulatory use of real-world evidence: when real is reliable. *Ther Innov Regul Sci.* 2018 May;52(3): 362-368.
10. Girman CJ, Ritchey ME, Zhou W, et al. Considerations in characterizing real-world data relevance and quality for regulatory purposes: a commentary. *Pharmacoepidemiol Drug Saf.* 2019; 28(4): 439-442.
11. Cowey CL, Mahnke L, Espirito J, et al. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Future Oncol.* 2017 Aug;13:1699–1710.
12. Anastassopoulos K, Farraye FA, Knight T, Colman S, Cleveland MV, Pelham RW. A Comparative Study of Treatment-Emergent Adverse Events Following Use of Common Bowel Preparations Among a Colonoscopy Screening Population: Results from a Post-Marketing Observational Study. *Dig Dis Sci.* 2016 Oct;61(10):2993-3006.
13. Velez FF, Anastassopoulos KP, Colman S, Shah N, Kauffman L, Murphy SM, Ruetsch C, Maricich YA. Reduced Healthcare Resource Utilization in Patients with Opioid Use Disorder in the 12 Months After Initiation of a Prescription Digital Therapeutic. *Adv Ther.* 2022 Sep;39(9):4131-4145.
14. Andrade, D. Real-World Data in Clinical Trials: Benefits & Privacy Risks. The Clinical Trial Vanguard. Sept. 2024. https://www.clinicaltrialvanguard.com/article/real-world-data-in-clinical-trials-benefits-privacy-risks. Accessed Sept 23, 2024.
15. Maniar, S. How real-world data and analytics help accelerate clinical trials. Google Cloud. June 2022. https://cloud.google.com/transform/real-world-data-platform-accelerates-clinical-trails-life-sciences-healthcare-clinica. Accessed Sept. 23, 2024.

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