Real-World Evidence Comes of Age

Whether for product development, to support clinical trial designs, for regulatory compliance, or for commercial purposes, real-world data and real-world evidence are helping to transform pharmaceutical decision-making.

The legal and regulatory environment is supportive of real-world data (RWD) and real-world evidence (RWE), which is expanding the use of these data sets in new ways. Under the requirements of the 21st Century Cures Act, the FDA was required to develop a framework and guidance for evaluating RWE for advancing the approval process with the objective of speeding up the process of bringing innovative products to patients in need. The act is designed to accelerate the development of new innovations and bring those to patients faster.

To date, the agency has been using RWD and RWE to monitor post-marketing safety and adverse events and to make regulatory decisions.

The FDA describes RWD as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources." Among these sources are electronic health records, claims data, product and disease registries, and patient-generated data from wearables, mobile devices, implants, etc. RWE, on the other hand, is the evidence derived from analysis of RWD.

The Role of RWE in Approvals and Reimbursement

Properly managed and understood, RWE could speed up drug development and positively impact the submission and approval process. So far, RWE has been used to support approvals for products to treat cancer and rare diseases.

In April 2019, the FDA approved the extension of Ibrance (palbociclib) combined with endocrine therapy for hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in men. This approval was based predominantly on analysis of RWD — from EHRs and post-marketing reports.

A year earlier, in March 2018, the agency fast-tracked the approval of blinatumomab (Blincyto), a second-line treatment for Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia, based on RWD analysis. And PD-L1 inhibitor Bavencio, from Pfizer and Merck, received approval to treat metastatic Merkel cell carcinoma after data was compared with historical control of matched patients.

Although the agency only rarely uses RWE to inform decisions on a product's effectiveness, it has established a framework for using RWE to assess possible changes in labeling about a product's effectiveness, including modifications to an indication. This framework includes determining whether RWD is fit for use, whether the design of a trial used to generate RWE provides adequate evidence to answer a regulatory question, and whether the study meets FDA requirements.

Acceptance of RWE for reimbursement purposes is less common; however, some agencies are placing more emphasis on RWE. For example, the French Transparency Commission does consider RWE regarding effectiveness within its overall reimbursement decision-making process. And RWE plays a key role in decisions about public funding for drugs in Poland.

Companies are using these data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice.

RWE in Clinical Trials

There is growing interest in using RWE in parallel with randomized clinical trials. While RCTs are the gold standard for informing regulatory decision-making, the size and diversity of the population involved in trials is too small to truly understand how a drug works in the real world. RWE helps to determine the longer-term effects of a drug, how a drug affects the broader population including those with comorbidities, the safety and efficacy of drugs that have been fast tracked, such as those to treat rare diseases, and the impact of adherence on outcomes.

The role of RWE in clinical trials is now well-accepted by regulatory authorities. The FDA has said RWD can help:

- Generate hypotheses for testing in randomized controlled trials
- Identify drug development tools (including biomarker identification)
- Assess trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, within a geographical area or at a trial site
- Inform prior probability distributions in Bayesian statistical models
- Identify prognostic indicators or patient baseline characteristics for enrichment or stratification
- Assemble geographically distributed research cohorts (e.g., in drug development for rare diseases or targeted therapeutics)

The agency does state that randomized controlled trials offer more rigorous scientific insights since, by definition, they prevent bias. However, the agency is evaluating the role of observational studies drawing on RWE in contributing to evidence of a product's effectiveness.

The challenge with RWD is ensuring the quality and validity of the data, although "big data" and advanced analytics capabilities are helping to address quality concerns. Another challenge is that in order to improve data quality, there needs to be more uniform access to real-world databases. However, privacy and data ownership concerns regarding access to large datasets make it harder to collect and share this data. Indeed, as Richie Etwaru, founder, CEO, and chairman of Hu-manity.co has said, questions over the ownership of data are at the core of the strained relationship between healthcare institutions and healthcare consumers.

Success in the future will depend on patients being included in the discussion about what data is used and how it is used. One organization that is seeking to advance that objective is rare diseases non-profit Global Genes, which has put together a four-part educational program to address this unmet need. It includes: the why's and how's of data collection; data trust and governance; how to develop collaborative research networks; and how to become a data-centric community.

A Commercial Proposition

Sources of RWD continue to expand and many public sector organizations as well as nonprofits and commercial businesses have compiled large data pools. Some countries have built large databases of millions of patients, including Japan, the United States (through Medicaid/Medicare claims databases), France, the UK, Germany, and Denmark. In addition, PatientsLikeMe and other online communities offer insights into patient conditions.

As the emphasis turns more and more to RWE, the market for RWE solutions continues to grow. The market was valued at $612 million in 2017 and is projected to reach $1.35 billion by 2023. According to a survey of 100 biopharma companies, IQVIA is considered the leader in RWD and RWE services.

Meanwhile, pharmaceutical companies are establishing processes and making organizational changes to address the increased focus on RWE. Companies are starting to invest more heavily in centralized RWE capabilities, with teams within medical affairs supporting a more robust approach to RWE.

Expanding the use of RWE will take greater industry and company-wide commitment. First, there will need to be greater understanding and communication about the value of RWE across the enterprise — from medical affairs to commercial to development to health and economics outcomes (HEOR). There also needs to be an operating model for integrating RWE, linked to milestones, an evidence plan, and governance process to manage risk from RWE activities. Third, collaborations, particularly with academic organizations to establish credibility and trust in analytics, will be crucial. And finally, there needs to be investment in platforms that can manage and analyze data quickly and cost-effectively.

EXECUTIVE VIEWPOINTS

Jaime Thompson
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Using RWE and RWD To Positively Impact Clinical Trials

Real-world evidence can be used from molecule to market. Global regulatory guidance is advancing to allow RWE in the development process. One use of RWD is development of an external comparator to gain approval for new indications of an existing drug. An example of this is our work supporting Pfizer Oncology to offer IBRANCE as a treatment option for male breast cancer patients where, due to the rarity of the disease, it is problematic to perform randomized clinical trials. RWE also enhances traditional trials by validating study protocols against available patient population and making enrollment efforts more targeted — all of which helps improve trial efficiency and getting the right therapies to market.

RWE and RWD for Product Positioning

Today's healthcare stakeholders need to understand the value of drugs as measured by patient outcomes. Whether it is an Integrated Delivery Network trying to understand their populations' needs or a payer trying to understand the relative drug effectiveness and budget impact, stakeholders across the ecosystem leverage traditional and emerging healthcare data sources. Phase 4 observational research allows us to continually examine the patient-centered endpoints to increase compliance and adherence — two challenges our industry has struggled to advance.

Katy Hewett
Associate Director, Research
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RWE and RWD to Identify Unmet Needs

Pharmaceutical companies can use RWD and RWE to first identify unmet needs in patient populations and support the development and approval of more treatment options. They can then use RWD and RWE to demonstrate the true value of those treatments and position them to payers, providers, and patients, encouraging positive reimbursement decisions, greater uptake, and adherence.

RWE and RWD Are Driving Innovation

The increasing opportunities that healthcare stakeholders have to provide RWD and RWE to supplement and contextualize clinical trial data are leading to accelerated development of RWD and RWE methodologies, particularly observational research. The need for data privacy, organized high-quality data, and patient-centric approaches that focus on authentic experiences are all driving the incorporation of a wider variety of research approaches into healthcare decision-making.