How real-world data is powering rare disease research

Part 2. RWD advances in Europe

Nadia Barozzi
Real World Data Strategy Director

Barbara Mascialino
Director, EU Real World Data Strategy

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As real-world data (RWD) transforms the drug development landscape, its power to advance research is becoming tangible in the most challenging therapeutic arena—rare diseases. In this series, Parexel experts discuss current initiatives in North America, Europe and China that are accelerating the use of RWD in rare disease research.

Leveraging RWD for rare disease research in Europe

Historically, rare diseases have not been a targeted area of biopharmaceutical research, but advancing scientific capabilities and growing awareness of the social impact of these conditions are giving rise to a new era in rare disease drug development. As many as 10,000 rare and genetic diseases have been classified, and while one rare disease may affect only a few patients, together they affect as many as 36 million people in the European Union.[1,2] The EU has implemented several Joint Actions to develop national information and data systems, and national rare disease plans. Advance work as also been initiated for rare cancers to improve diagnosis, care and treatment of patients with these rare diseases through the pooling of resources and cooperations.[1]

Regulations and incentives supporting rare disease research. In the last few decades, patient communities, health care professionals and policy makers have encouraged the expansion of research into rare diseases to ensure that patients with rare conditions have access to the same quality of treatments as those with more common diseases.[1]

In 1999, the European Medicine Agency (EMA) adopted legislation on rare diseases; Regulation (EC) No 141/2000 aimed at fostering the development of orphan medicinal products designed to treat life-threatening or very serious conditions that affect no more than five in 10,000 people.[3] The regulation acknowledges the challenge pharmaceutical companies face in rare disease drug development and provides incentives including 10 to 12 years of market exclusivity and fee reductions for regulatory procedures. The regulation also established the Committee for Orphan Medicinal Products (COMP) to evaluate applications and provide guidance for orphan status.

Dramatic progress fostered by regulation and advancing technologies. Since the adoption of Regulation (EC) No 141/2000, more than 260 orphan-designated medicines have been authorized in Europe.[3] Between 2000 and 2021, the EMA assigned the orphan designation to over 1,900 medicines.[4]

"The increase in advanced technologies and methodologies—notably, next-generation sequencing (NGS) and personalized therapeutics targeted to an individual's patient profile—have contributed greatly to this progress," says Barbara Mascialino, Director, EU Real World Data Strategy. "The adoption of RWD promises to accelerate advances in rare disease research." The establishment of patient registries and the utilization of RWD have enhanced our understanding of the natural history of rare diseases and the overall patient journey. These data sources help identify disease patterns, treatment outcomes, and long-term effects, which are critical for designing effective clinical trials and product development.

While diverse and innovative sources of RWD can support clinical research challenged by the limited availability of rare disease patients, national and international rare disease patient registries are most common source of RWD. Registries have the advantage of providing richer and better fit-for-purpose data for complex studies that require advanced data granularity—lab results, patient reported outcomes, biological or genetical data.

Rare disease registries managed by patient advocacy groups and medical institutions focusing on a particular rare condition have become vital resources. In the EU, registry data have been used in natural history studies and to create external control arms (ECAs). ECAs have supported single-arm clinical studies in rare diseases applications that have been successfully submitted for product approval.

EMA regulatory initiatives to support RWD use. The use of RWD in clinical research is increasingly accepted by EU health authorities—especially in areas of high unmet medical needs, or when there is an evidence gap in the clinical practice.

In 2015, the EMA introduced an initiative to explore a systematic and standardized approach to the use of registry data in evaluating benefit-risk in drug development.[5] In 2021, EMA issued the *Guideline on Registry-based Studies* to address the methodological, regulatory and operational aspects involved in using registry-based studies to support regulatory decision-making.[6]

EMA and the European Medicines Regulatory Network (EMRN) also established a coordination center to provide timely and reliable evidence from real world healthcare databases across the European Union. This capability is called the Data Analysis and Real-World Interrogation Network.[7] DARWIN EU established an expanding catalogue of observational data sources for use in medicines regulation to provide a source of high-quality, validated RWD on the uses, safety and efficacy of medicines.

DARWIN EU also addresses specific questions by carrying out high-quality, non-interventional studies, including developing scientific protocols, interrogating relevant data sources and interpreting and reporting study results.[7] Currently, 39 data sources from 16 European countries are part of the DARWIN EU initiative with over 182 million patients providing data. The network is growing, and it is expected that by the end of 2025 approximately 40 data sources will be part of the network.[8]

Growing RWD research collaborations in Europe. The EMA-fostered registry framework has incentivized collaboration among registry coordinators, healthcare professionals, patients' associations, academic institutions, and users of RWD in fields of drug development—pharmaceutical companies, regulators and reimbursement bodies. Since 2015, many national and international registries have been established and expanded across Europe.

Examples based in Europe include registries focused on cystic fibrosis and Huntington's disease. The European Cystic Fibrosis Society Patient Registry (ECFSPR) collects data on cystic fibrosis patients across Europe, providing insights into disease epidemiology, treatment outcomes, and the impact of new therapies.[9] The European Huntington's Disease Network (EHDN) registry collects data on patients with Huntington's disease, enabling research on disease progression and the effectiveness of treatments.[10]

Numerous international registries now provide RWD for European researchers. The Translational Research Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) Global Registry Network comprises independent neuromuscular diseases (NMD) patient registries from around the world. This federated network currently has 65 registry members (either NMD- or disease-specific), who collect data on approximately 88,800 NMD patients.[11] The World Bleeding Disorders Registry (WBDR) collects data from approximately 11,500 participants enrolled at 115 centers across 44 countries worldwide.[12]

With hundreds of national and international registries now providing RWD sources, the EU has established the European Platform on Rare Disease Registration to help manage the fragmentation of rare disease information.[13] The platform makes national registry data searchable and supports standards for rare disease data collection and exchange.

To date, 11 research projects on rare diseases have been funded through Horizon Europe, the research and innovation program of the EU. These wide-ranging projects include identification of gene therapies; drug development or repurposing; and development of a comprehensive regulatory framework for regulatory decision making. In the next five years, all of these projects are expected to deliver cutting-edge technologies, to increase awareness and to provide patients and their families with state-of-the-art knowledge and treatments.[14]

Success stories: RWD in rare disease submissions. The value of RWD in rare disease drug evaluation is highlighted by the EMA approvals of two novel therapies—blinatumomab (Blincyto) and avelumab (Bavencio).

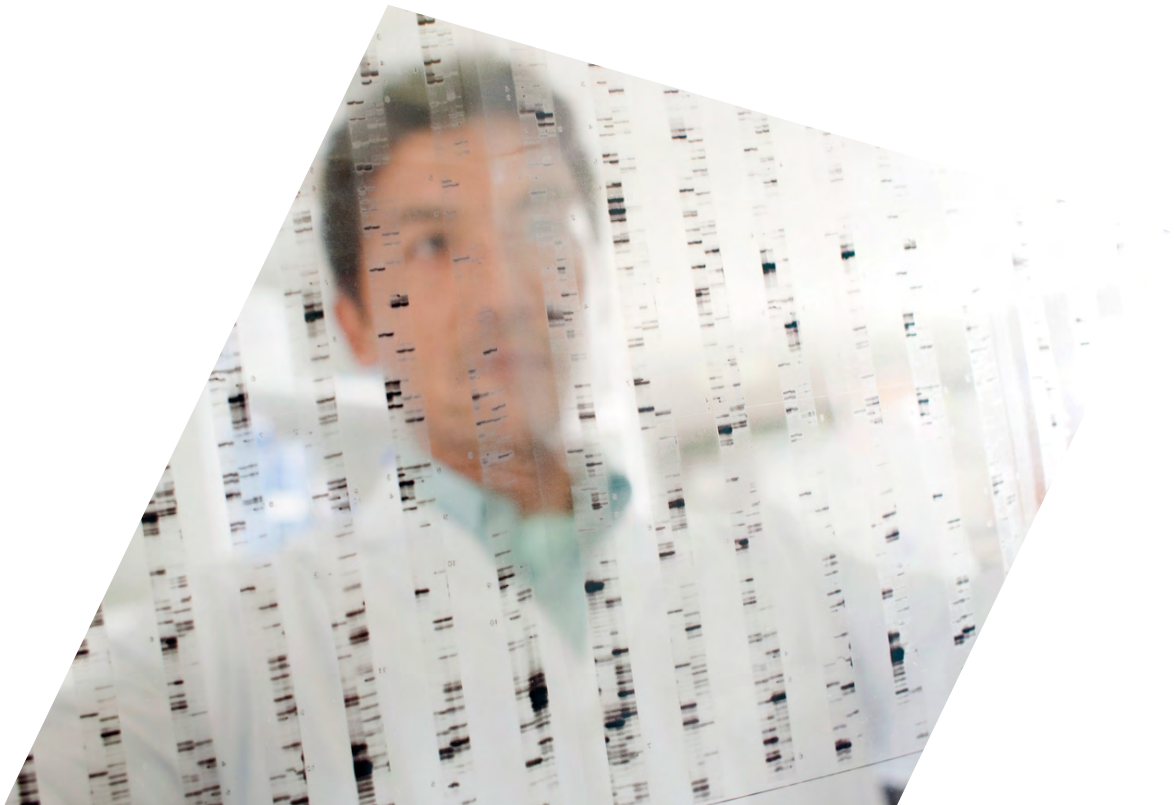
Blinatumomab was approved by EMA in 2015 for the treatment of adults with Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph− ALL); European introduction followed FDA approval in 2014. Both EMA and FDA regulatory submissions included a Phase 2, single-arm trial with an external control arm as supplemental evidence. The ECA, built from a historical database from Europe and U.S. study sites, intended to provide a relative measurement of complete remission and overall survival between blinatumomab in the experimental arm and standard of care in the external arm. The ECA positively influenced the approval decisions of both agencies.[15]

Avelumab was approved by both the EMA and the FDA 2017 for the treatment of patients (adults and children in the US; adults only in Europe) with metastatic Merkel Cell carcinoma (mMCC). The submission included a single-arm study and an ECA, based on a retrospective chart review and registry data; these data were used to characterize the natural history of mMCC treatment outcomes and to assess the risk-benefit profile of the product. The ECA still influenced the approval decision, despite the lack of a formal statistical comparison between the ECA and the clinical trial, and missing ECA patient data (e.g., Eastern Cooperative Oncology Group [ECOG] performance score, life expectancy, and previous therapies).[14]

Barriers. RWD on rare diseases typically are scattered across multiple sources. Inoperability hampers applications for EU research as it does worldwide. Multiple, fragmented sources are not the only barrier to RWD evidence generation, however. Additional bottlenecks include lack of data harmonization, small patient sample sizes, and the heterogeneity of diseases, healthcare systems, and disease management. Collectively, these factors make evidence generation extremely complex.

Novel designs: Parexel's RWD-enriched PASS study. At Parexel, we are currently conducting a non-interventional post-authorization safety study (PASS) mandated by EMA to monitor the safety profile of a product used to treat a rare neurological disease. In this novel design, data from an international disease registry will be ingested in a platform and combined with data collected prospectively to create a unique dataset.

"While the study design is bringing operational challenges, this is a unique opportunity to demonstrate how RWD can support regulatory studies," Mascialino notes. "Using a similar approach, three multi-database PASS studies are accessing databases across Europe and Israel and have been allowed to obtain data on two distinct rare disease populations in order to comprise a sample large enough to produce medical evidence."



What we will see in the near future. According to a recent market analysis, the 2024 global real-world evidence (RWE) solutions market size was valued at 17.91 billion USD. The market projected to grow from 20.03 billion in 2025 to 48.02 billion by 2032—a compound annual growth rate of 13.3%.[16]

"Consistent with this growth, we can expect increasing use of registries to collect comprehensive and longitudinal patient data," Mascialino says. "Use of RWD in rare diseases research in Europe will be driven by advancements in data collection technologies, regulatory frameworks, and collaborative efforts."

In the next few years, we will see ongoing efforts to harmonize regulatory frameworks across European countries to streamline RWD collection and use, ensuring consistency and compliance with privacy laws such as the General Data Protection Regulation (GDPR). The development and adherence to robust ethical guidelines will evolve and will bring more clarity on the data journey, protecting patient privacy while ensuring data integrity.

Immediate efforts focus on developing standardized data formats and terminologies to facilitate RWD sharing and interoperability across different healthcare systems and research platforms. The goal is to create interoperable health information systems that enable seamless data exchange between stakeholders. We will see strengthening collaborations between European countries, research institutions, and pharmaceutical companies. The growth of RWD sharing and research applications will improve the collective understanding of rare diseases and support greater patient involvement to ensure that their perspectives and experiences are integral to rare disease studies.

Advanced data technologies such as artificial intelligence (AI) and machine learning (ML) will soon play a crucial role in the collection and application of RWD. AI technologies will be harnessed to automate and improve precise patient identification and data integration from various sources, such as EHRs and wearable devices.

Emerging AI tools, including generative AI and large language models, will also improve data analysis, providing capabilities including pattern recognition and outcome prediction while preserving ethical and privacy standards. Wearable devices and remote monitoring tools will also be better integrated to capture real-time health metrics and patient-reported outcomes.

Predictive analytics will advance personalize treatment plans for rare disease patients, uncovering novel insights and facilitating the discovery of new therapeutic targets. Integration of genomic data with RWD will enhance understanding of the genetic underpinnings of rare diseases and support personalized medicine approaches used to identify patient subgroups that may benefit from specific therapies based on their unique genetic and clinical profiles.

Given the impact of RWD on this future, it will be crucial to Invest in educating and engaging the rare disease community—patients, healthcare professionals, and policymakers—about the value and use of RWD. In this emerging RWD-driven landscape, Europe is poised for significant advancements, with a strong focus on leveraging technology, fostering collaboration, and ensuring ethical and regulatory compliance. These efforts will collectively contribute to better understanding, diagnosis, and treatment of rare diseases, ultimately improving patient outcomes and quality of life.

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Parexel International Corporation
2520 Meridian Pkwy, Durham, NC 27713, USA
+1 919 544-3170
Offices across Europe, Asia, and the Americas
www.parexel.com

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