Ingenious Brain

Future-Proofing Businesses

Whitepaper

The Clinical Trial Alone Isn't Enough:

Why Rare Disease Development Needs Real-World Evidence

Introduction

Rare diseases affect more than 300 million people worldwide and remain one of the largest areas of unmet need in global health. More than 1 billion individuals are directly affected when families and caregivers are taken into account, and the yearly worldwide cost is projected to be more than $7 trillion. Approximately 95% of the over 7,000 uncommon diseases currently lack accessible therapies. This highlights the substantial unmet need and explains why 44% of clinical trial pipelines in the US and Europe focus on orphan illnesses.

The most common therapeutic areas represented by orphan drug designations were: oncology (38%), neurology (14%), and infectious diseases (7%). Initial orphan drug approvals followed a similar therapeutic area pattern: oncology (38%), infectious diseases (10%), and neurology (10%). The top 15 diseases accounted for 25% of all designations, and the top 68 diseases accounted for 50% of all designations.

Over the past ten years, one of the most active areas of pharmaceutical innovation has been rare disorders. Opportunities to create cures for diseases that were previously thought to be incurable have greatly increased thanks to developments in genome sequencing, precision medicine, and cell and gene therapies. Even though only a small percentage of people are afflicted by each rare disease, their combined effect on public health is significant.

According to studies, people with uncommon diseases often have to wait four to five years for a proper diagnosis, during which time they may see several different medical professionals, go through pointless tests, or be treated inappropriately. In addition to worsening illness outcomes, these delays limit options for prompt care and clinical study involvement.

Real-world data (RWD) is increasingly being utilized to support rare illness regulatory, HTA, payer, and post-launch choices, as conventional trials are sometimes hampered by small patient groups and short follow-up.

A common issue in rare diseases is a trial design that is randomised for a period, before patients enter some kind of long-term extension study. This does not have a comparative arm, but it does provide longer term outcomes data (but it takes years to accumulate and hence gives payers uncertainty). This is difficult since many uncommon illnesses lack basic natural history information and over 95% of them have no approved treatment.

For rare disease launches, Real-World Evidence (RWE) can assist in filling the gaps in natural history, comparative effectiveness, long-term safety, therapy durability, and patient-relevant outcomes.

Overview

Rare diseases trials accounted for most disease trials over the years across key markets. Although rare diseases may affect only a small portion of the population, they have an outsized influence in clinical research. Clinical trials for rare diseases are quickly rising globally, accounting for more than 45% of all trial starts. Outside of special regional or national legislation (such as the Orphan Drug Act in the US), this expansion is driven by a combination of scientific breakthroughs, economic incentives, and patient-centered trial designs.

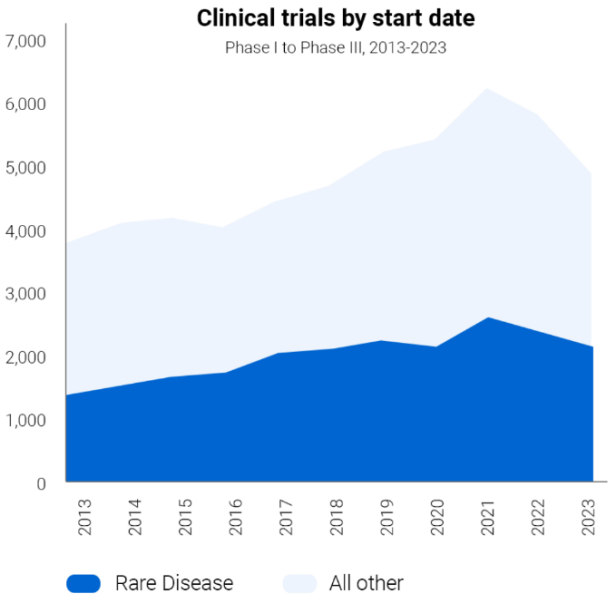

Fig 1: Growth rate of rare disease clinical trials relative to other therapeutic areas

Clinical data in rare diseases originates from tiny, short-term RCTs or single-arm trials. Hence, RWE and historical controls are employed to bolster the evidence base.

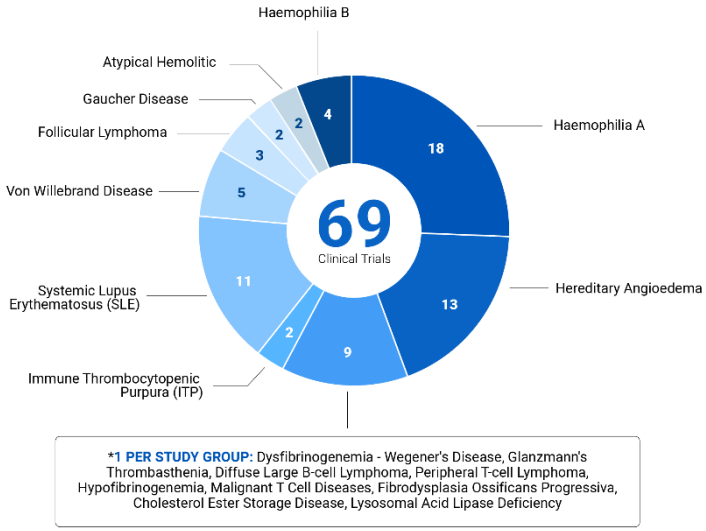

Fig 2: Distribution of clinical trials based on rare diseases

Rare disease medicines account for a significant portion of all new drug approvals. almost the last five years, orphan medications have accounted for almost half of new active substance approvals in the US and an average of 45% in Europe. Even the patient populations for rare diseases is underdiagnosed, geographically distributed in small clusters, and clinically varied, making it challenging to generate evidence.

Key Forces Driving This Shift Are:

a. **Scientific Breakthroughs**

Advances in genomic sequencing and molecular diagnostics have significantly increased our understanding of the underlying causes of uncommon diseases, many of which are monogenic and respond effectively to focused interventions. New technologies, such as RNA-based therapeutics and tailored biologics, are allowing researchers to look beyond symptom relief and directly at the underlying causes of uncommon disorders.

b. **Patient Advocacy and Data Infrastructure**

Patients and caregivers take a more active part in furthering rare illness research. Clinical researchers can better understand where patients are and how to approach them thanks to digital tools, disease-specific registries, and patient-led initiatives.

c. **Increased Biotech Investment**

Many small- to medium-sized biotech businesses prioritize uncommon diseases as part of their main development strategy. These businesses are frequently built around highly targeted assets and operate with greater speed and flexibility than larger pharmaceutical enterprises.

d. **Regulatory Support**

Regulatory bodies around the world have created systems to mitigate the financial risk of developing medicines for rare diseases. In the United States, the Orphan Drug Act offers tax breaks, waived user fees, and prolonged market exclusivity for approved therapies. Similar policies exist in other locations to encourage international investment.

The methodological gap between rare disease and standard clinical trials shows up at nearly every stage of development, from recruitment through post-market surveillance. These differences shape how evidence is generated, interpreted, and ultimately accepted by regulators and payers.

Key differences	Rare disease clinical trials	Standard clinical trials
Patient population and recruitment	Small, geographically dispersed, and challenging to recruit.	Large, often centralized, easier to recruit.
Trial design and methodology	Requires adaptive, single-arm, or crossover designs.	Standardized with randomized controlled trials.
Data collection and analysis	Limited data, reliance on natural history studies, and small sample sizes.	Robust data, large sample sizes, extensive statistical analysis.
Regulatory pathways and approval	May benefit from orphan drug status, and fast-tracked reviews.	The standard regulatory process is often more time-consuming.
Market entry and commercialization	Niche market, high pricing potential, targeted marketing.	The broad market, competitive pricing, and mass marketing.
Ethical considerations	Emphasis on access, compassionate use, and patient advocacy.	Emphasis on broad safety, and long-term efficacy.
Funding and investment	Often relies on grants, philanthropic funding, or government incentives.	Typically backed by large-scale pharmaceutical investment.
Collaboration and partnerships	High collaboration with patient advocacy groups and specialized centers.	Standard industry partnerships with large-scale healthcare providers.
Regulatory flexibility	More flexible due to the nature of the diseases, the potential for conditional approvals.	Standardized, with strict regulatory requirements.
Outcome measures	Focused on biomarkers or surrogate endpoints due to small populations.	Focused on clinical outcomes and long-term efficacy.
Post-market surveillance	Require extensive long-term follow-up due to limited initial data.	Standard post-market surveillance with established protocols

Table 1: Key areas where clinical trials for rare diseases differ from those for common diseases.

Methods for Modular Framework

To address the key differences outlined above, we developed a modular framework grounded in a structured, stepwise methodology. The approach pairs a targeted literature synthesis with practical, illustrative validation, keeping the framework scientifically rigorous while remaining adaptable across disease areas. The steps below outline how the framework was built and tested.

Fig 3: The modular framework, from targeted evidence search through conceptual validation

Key Evidence Generation Strategies by Leading Companies

Several leading pharmaceutical and biotechnology companies have embedded RWE into their rare disease strategies, spanning early evidence generation through post-launch surveillance. Their approaches vary widely, from multi-decade patient registries to AI-enabled data integration and multi-stakeholder collaboration models. Together, they illustrate how the industry is applying RWE across the full rare disease lifecycle.

Organization / Initiative	How RWE is Used in Rare Diseases	Key Highlights
sanofi	Long-term global rare disease registries	• >30 years of registry experience • ~15,000 patients included • Supported >100 peer-reviewed publications • Used to study disease biology, treatment outcomes, monitoring, and clinical guidelines
ALEXION	RWE, patient registries, and natural history data	• Supports regulatory decision-making • Addresses fragmented data in small, underdiagnosed patient populations • Improves understanding of disease progression
Takeda	Patient-centered RWE and AI integration	• Incorporates patient perspectives, RWE, and AI into rare disease trials • Takeda Canada–Pentavere collaboration generated one of the world's largest HAE (normal C1 inhibitor) RWE datasets
BIOMARIN	Post-marketing RWE and natural history comparisons	• Multiple RWE studies for **VOXZOGO** in achondroplasia • Uses ongoing extension studies and natural history data to support post-marketing evidence requirements
SAREPTA THERAPEUTICS	Longitudinal RWE in Duchenne muscular dystrophy (DMD)	• Nearly 10 years of RWE collected • Plans to incorporate RWE with confirmatory trial results in regulatory submissions
RWE4Decisions	Multi-stakeholder RWE framework	• Brings together HTA bodies, payers, regulators, clinicians, patient groups, registry holders, industry, and academia • Aims to strengthen the use of RWE in payer and HTA decision-making

Table 2: RWE strategies and key highlights from leading rare disease drug developers

Sanofi has been developing rare disease registries for more than 30 years, collecting real-world data for the global rare disease community and supporting over 100 peer-reviewed publications.

Sanofi's rare disease registries contain RWD from approximately 15,000 people, which has aided research into disease biology, treatment outcomes, monitoring, and treatment guidelines. Alexion claims that it employs real-world evidence, patient registries, and natural history data to influence regulatory paths in rare disease drug development.

Alexion also emphasizes that rare disease research frequently relies on fragmented data due to small, underdiagnosed populations and insufficient understanding of disease development. Takeda is redesigning rare illness trials and improving patient access by incorporating patient perspectives, RWE, and AI.

Takeda Canada collaborated with Pentavere to generate RWE in hereditary angioedema, providing one of the biggest cohort datasets worldwide for HAE with normal C1 inhibitor.

BioMarin presented various RWE studies for VOXZOGO in achondroplasia and employs ongoing extension studies compared to natural history to support post-marketing evidence requirements.

Sarepta has cited nearly a decade of real-world evidence in Duchenne muscular dystrophy and intends to include confirmatory trial results from RWE in regulatory applications.

RWE4Decisions is a multi-stakeholder program that involves HTA bodies, payers, regulators, doctors, patient groups, registry holders, industry, and academics to improve RWE use in payer and HTA decisions.

Roadblocks to Generating Clinical Evidence

Generating credible clinical evidence in rare diseases is shaped by structural constraints that differ fundamentally from common disease research. These roadblocks span the full evidence journey, from patient identification through regulatory and payer engagement.

Fig 4: Roadblocks in Evidence Generation and Interpretation Related to Rare Diseases

The most significant RWE problem for rare disease launches is data fragmentation across EHRs, claims, registries, provider notes, and genetic databases.

Developing and releasing treatments for rare diseases presents significant obstacles, including **tiny patient populations, poor disease understanding, little evidence, and unclear regulatory processes**.

- Small sample numbers make it difficult to create cohorts, analyze subgroups, compare evidence, and build statistical confidence.
- HTA and reimbursement decisions are questionable because to limited natural history data and a lack of disease-specific outcomes.
- Single arm studies and a lack of comparison data make it difficult to demonstrate relative efficacy over standard of treatment.
- Budget impact and cost-effectiveness modeling are still questionable because rare disease launches sometimes have limited long term outcomes and tiny evidence packages at the outset.
- Patient centered outcomes are crucial because rare diseases affect patients differently. Registries can capture symptoms, disease burden, and lived experience throughout time.
- Trial design and enrollment are difficult and far from the ideal double-blinded, comparative, parallel design of gold-standard randomized clinical trials because of the limited target population and the severity of most rare diseases.
- Evidence generation is made more difficult by the heterogeneity of rare disease and the possibility of co-morbidities among trial participants.

In order to receive regulatory approval, manufacturers wishing to create an orphan medication or technology frequently need to consider the needs for pediatric medications early on.

Five key challenges hindering widespread adoption of RWE use by US payers.

Fig 5: Five key challenges limiting RWE adoption among US payers

Practical challenges with evidence-creation requirements *(such as the CED and MEA systems)*

In the United States, the Centers for Medicare & Medicaid Services (CMS) has a designation of CED, in which CMS may determine that coverage for a drug or device is limited to the context of a clinical study, with the intention to revise the coverage decision based on the results of the studies conducted.

In Europe, RWE is an important component of MEAs, which are agreements reached between payers or pricing and reimbursement bodies and manufacturers to allow the introduction of new pharmaceuticals and other health innovations into the healthcare system. CED and MEAs are similar in that a technology is given a conditional reimbursement decision based on a commitment to collect more data, to reduce either financial or clinical uncertainty.

The European Commission released new guidelines in July 2024 to define orphan devices and solve some of the difficulties experienced by producers of medical devices recommended for use in rare diseases.

RWD sources in Japan (until September 2020) through a targeted literature review (e.g., MEDLINE) and institutional knowledge. The study comprised administrative claims, electronic medical records (EMR), and general population-based surveys. Therapeutic area-specific surveys and registry data were removed due to their specialized nature and limited generalizability to the total population. The data properties and constraints of the selected sources were reported descriptively.

Japan's health system and corresponding healthcare databases are distinct, and RWD sources are based on claims and/or EMR data.

Category	Available Databases / Sources
Hospital-based	NHO NCDA, NHO MIA, 4DN, HCEI/RWD, LDI, MID-NET, MDV HB, JMDC HB, NDC
Insurance-based	NDB, JMDC PB, JammNet, MinaCare, MDV PB, Medi-Scope
Pharmacy-based	Medi-Trend, JMIRI, IQVIA NPA data, Nihon-Chouzai PFR
Others	NHWS, PatientsMap

Abbreviations: NHO: National Hospital Organisation; NCDA: NHO Clinical Data Archives; MIA: Medical Information Analysis; 4DIN: a hospital based database owned by 4DIN; HCEI/RWD: Health, Clinic, and Education Information Evaluation Institute / Real-World Data; LDI: Life Data Initiative; MID-NET: Medical Information Database Network; MDV: Medical Data Vision; HB: Hospital Based; NCD: National Clinical Database; NDB: National Database of Health Insurance Claims and Specific Health Check-ups; PB: PayerBased; JMIRI: Japan Medical Information Research Institute ; NPA: National Prescription Audit; PFR: a pharmacy-based database owned by 4DIN; NHWS: National Health and Wellness Survey Database

Table 3: Real-world data sources and database categories within Japan's healthcare system

The number of databases available worldwide is growing as the importance of real-world evidence (RWE) rises. The growing interest in Asia-Pacific RWE creates a problem in comprehending the potential and limitations of new databases.

Sources of RWD include hospitals (41%), insurance (27%), pharmacies (23%), and surveys (9%).

Outpatient visits account for 82% of the data, with drugs supplied accounting for 64%. Sixty-four percent of databases include inpatient stay data, while 59% include information on medication provided in-hospital. The Medical Data Vision (MDV) and JMDC databases are commonly utilized in industry-sponsored studies to analyze treatment patterns and resource utilization.
Pharmaceutical companies have access to the majority of the healthcare databases in Japan.

The limitations of the selected databases are:

- Access restrictions.
- Potential loss of follow-up when patients visit several healthcare institutions .
- Under-recording death data
- Possible missing data in inpatient records.
- Restricted populations (e.g., just working people)
- Non-specific date information (e.g., month instead of day)
- Language barrier (e.g., documentation and data dictionaries)

The Evolving Role of RWE

Fig 6: The role of real-world evidence across the rare disease development and regulatory journey

- **The essential role of diverse RWE sources**

Real-world evidence (RWE) is a crucial component of the RDEP review process because it can help sponsors assess if a program is eligible by establishing that an illness meets the ultra-rare prevalence requirement. This can be especially useful for illnesses that are underdiagnosed, inconsistently classified, or clinically diverse. Once RDEP eligibility is confirmed and development begins, RWE can continue to play an important part in the evaluation process:

- Patient registries can aid with patient identification and longitudinal data collecting.
- Natural history studies can assist in determining disease development in untreated patients.
- When randomization is not possible, external control arms made of high-quality RWD can help to strengthen causal inference.
- Post-marketing RWE can be used to assess a therapy's safety and efficacy in real-world situations.

- **RDEP's role in discovering medicines for extremely uncommon diseases**

The FDA implemented the RDEP method to promote clarity and predictability in the construction of evidence packages for ultra-rare illness medicines. It formalizes the concepts described in FDA guidance and earlier approvals, as well as providing a clear method for early, focused communication between sponsors and regulators about the evidential approach.

RDEP is designed for development programs that satisfy all of the following requirements:

- The target disease is caused by a known inborn genetic abnormality.
- The targeted disease affects less than 1,000 persons in the United States. The disease's complications are life-threatening, fast progressing, and there is no current therapy to change the disease's course.
- The sponsor can fairly establish the therapy's efficacy with one adequate and well-controlled study and strong confirmatory data.

Ingenious e-Brain's Strategic Consulting Services Across the Value Chain

We help pharmaceutical and biotech companies navigate the evidence generation challenges unique to rare diseases, combining scientific depth with commercial strategy. Our methods for sourcing, structuring, and analyzing real-world data are customizable and scalable, tailored to each client's therapeutic focus and research objectives.

Rare disease evidence must satisfy a broad set of stakeholders, including regulators, HTA agencies, payers, healthcare professionals, and patient communities, often across the full product lifecycle. We support clients in designing and executing evidence generation strategies that meet these varied requirements, from early clinical development through post-launch value demonstration.

Our capabilities include:

- **Evidence generation strategy**
- **Study design**
- **RWE studies**
- **Patient registry development**
- **Comparative effectiveness research**
- **HEOR**
- **Market access support**
- **HTA dossier development**
- **Publication**
- **Competitive Intelligence**
- **Launch evidence planning**

Conclusion

Rare diseases afflict over 300 million people worldwide, but over 95% currently lack licensed medicines, making evidence production a significant problem. Small, geographically distributed patient groups, inadequate natural history data, and a dependence on single-arm or short-duration trials all constrain conventional clinical research.

RWD and RWE utilization in rare disease drug development provides an opportunity to efficiently handle some of the most difficult research challenges, such as defining disease features, optimizing clinical trial designs, gathering essential patient perspectives, and navigating regulatory landscapes. Companies that incorporate these methods in their development plans will increase their research, improve patient outcomes, and gain successful market entry.

RWE has emerged as a critical component of clinical trials, assisting with patient identification, natural history investigations, external control arms, long-term safety, and post-marketing reviews.

Leading players such as **Sanofi, Takeda, Alexion, BioMarin,** and **Sarepta** are incorporating registries, longitudinal studies, and patient-centered RWE into their development methods. RWE is changing rare disease medication development by offering the knowledge required to address unique challenges. As the health care landscape evolves, RWD and RWE will remain critical in fostering innovation and providing life-changing medications to patients living with rare diseases.

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