

# Overcoming the Challenges of Rare Disease Drug Development



## Contents

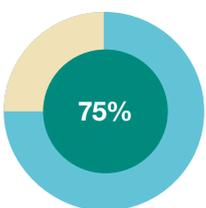
---

Overcoming the Challenges of Rare Disease Drug Development	3
Challenge 1: Enrolling, Engaging, and Retaining Patients	4
Challenge 2: Designing and Evaluating Clinical Trials	6
Challenge 3: Ensuring the Quality of Patient Data	7
Challenge 4: Navigating Global Regulatory Requirements & Gathering Payer Evidence	8
Therapeutic Experience	10

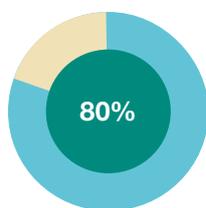
## Overcoming the Challenges of Rare Disease Drug Development

Characterised by small, highly heterogeneous patient populations. Rare diseases are usually genetic and therefore chronic. Rare disease trials can often magnify the challenges typically associated with traditional studies.

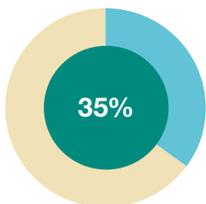
An estimated 350-400 million people worldwide suffer from rare diseases. Cumulatively, rare diseases are estimated to affect 1 in 17 people.



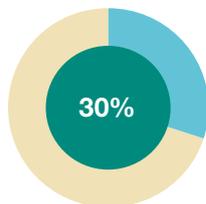
75% of rare diseases affect children



80% of rare diseases are linked to genetic mutations



Rare diseases are responsible for 35% of deaths in the first year of life



30% of children with rare diseases will not live to see their 5<sup>th</sup> birthday

## Orphan drugs

Licensing of medicines for rare diseases, often referred to as ‘orphan medicines’ or ‘orphan drugs’ is coordinated by regulatory agencies such as the FDA, the EMA and the Japanese Ministry of Health, Labour & Welfare. Sponsors must first apply to the relevant regulatory agency for ‘orphan designation’. Once a drug receives an orphan designation, the sponsor can avail of a number of incentives for further development of the drug.

With an estimated 7,000 rare diseases worldwide, what constitutes “rare” differs from region to region:

### EU

Treats diseases with a prevalence of no more than 5 cases per 10,000 individuals

### US

affects fewer than 200,000 people  
i.e. Prevalence of < ~6.25 per 10,000 individuals

### Japan

Is intended for use in less than 50,000 patients in the country  
i.e. Prevalence of < ~4 per 10,000 individuals

### China

Currently, there is no regulatory definition or specific policy for rare diseases - so there are no grants, financial assistance or marketing exclusivity for orphan drug development.

However, regulatory policy in China is trending to use the same standard as ICH regions, and there is some scope for priority reviews for products with significant clinical value and/or prevention and treatment of certain diseases such as HIV, Tuberculosis, Hepatitis and Rare Diseases.

## Orphan drug development

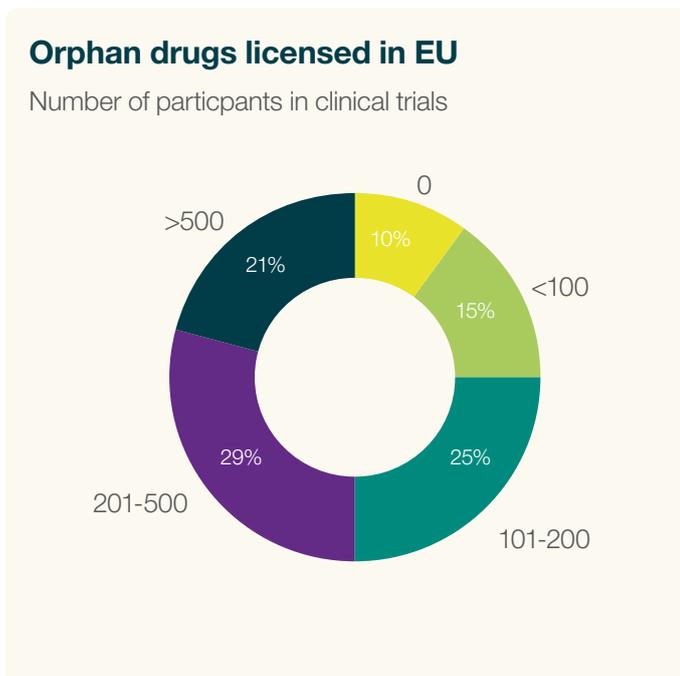
Successful development requires a partner that can help sponsors:

- Identify and support suitable sites
- Enrol, engage, and retain qualified patients
- Design a clinical trial that is both scientifically robust and patient-centric
- Facilitate the collection of high quality patient data that satisfies global regulatory and payers requirements

## Challenge 1: Enrolling, Engaging and Retaining Patients

As some rare diseases affect very few patients worldwide, finding, engaging, and enrolling individuals who qualify for a particular study is especially difficult. Patients with a specific condition are spread globally, and specialists in rare diseases are limited.

This limitation is partly due to the fact that many patients impacted by rare diseases are children. In addition to the number of ethical dilemmas associated with paediatric studies, recruiting challenges are intensified because sites are often research naive, requiring additional assistance and/or training from the sponsor or CRO, as well as technological tools to enhance patient engagement. While applying traditional study design methodologies may yield a scientifically robust trial, the resulting protocols could hinder recruitment due to treatment burden for patients who may be very ill, disabled and/or traveling long distances. Flexible and adaptable approaches must be taken to minimise the burden to patients and their families.



Currently, 54% of clinical trials for orphan drugs that are licensed in the EU have enrolled fewer than 500 participants.

Clinical trials of orphan medicines  
Buckley, Brendan M  
The Lancet; Jun 14-Jun 20, 2008;

## Solutions & Next Steps

### Build relationships with patient advocacy groups

Rare disease patient advocacy groups are becoming an increasingly valuable resource for engaging with patients eligible for clinical trial participation. These include disease specific advocacy groups that may be international or region specific, in addition to the US National Organization for Rare Disorders (NORD) and the European Organization for Rare Diseases (EURODIS). EURODIS, for example, represents 724 rare disease patient organisations in 64 countries.

Patient Advocacy Organisations are emerging as major contributors to the drug discovery process and can often determine the evolution of a product, influence protocols, and advocate for the approval of beneficial treatments. Relationships with these groups can help drug developers access patients and earn the support needed to conduct a clinical trial.

### Enhance engagement with patient-centric tools

The ability to retain patients is vital to the success of a rare disease clinical trial. Patient attrition, especially within orphan drug development, puts a strain on a study's data quality. Rare disease researchers must provide prospective participants with practical support and access to clear and comprehensive clinical information that enhances understanding and, consequently, retention.

## FIRECREST

FIRECREST is a multi-award winning web based suite of digital products designed to enhance patient engagement and support investigators, patient recruitment and retention. It is deployed for more than 1,000 studies with over 440,000 active users, including the top 10 global pharmaceutical companies, and comprises several solutions.

Firecrest Patient eConsent employs easy-to-understand videos and visual aids to explain the complex scientific concepts and medical terms that are found in initial protocols. Multimedia materials are designed with evidence-based research from Carnegie Mellon University, which greatly enhances patient knowledge, recruitment and retention – particularly for children.

Despite intensive and costly monitoring, 5% of all FDA findings are due to errors in the consenting process. Firecrest's eConsent virtually eliminates these errors while providing a real-time view of your trial compliance.

[ICONplc.com/econsent](https://www.iconplc.com/econsent)

## High precision site qualification and patient selection through innovative initiatives



### Genomics England

ICON is proud to have been selected by Genomics England as the Data Management Partner for the 100,000 Genomes Project which seeks to sequence 100,000 genomes – 50,000 for cancer and 50,000 for rare disease indications – from 70,000 patients, with medical histories that total millions of data points.

This will enable more precise identification of subpopulations and enhance patient registries, and critically for patients, the hope of much earlier diagnosis of their illness.

Watch our video at:  
[ICONplc.com/genomics](https://iconplc.com/genomics)



### Electronic Health Records (EHRs)

ICON is advancing site selection and patient recruitment by enabling customers to access extensive real-time patient data and physician notes, found in over 100 million electronic health records from the following sources:

- IBM Explorys
- EHR4CR  
(European Health Records for Clinical Research)
- TriNetX

In partnership with IBM Watson & Explorys, we are pioneering patient recruitment solutions that leverage cognitive computing to transform clinical trial matching. The trustworthy interrogation of EHRs enables ICON to use a data-driven approach to find the right patients for trials.

In addition ICON's bespoke methodology, PRAEVISIO, validates site access prior to selection:

- Reduces the number of non-performing sites
- Supports site team to build cohort of patients prior to initiation
- Support sites to start recruitment soon after SIV

[ICONplc.com/ehr](https://iconplc.com/ehr)



### Site Selection

Sites providing treatments for rare diseases are generally highly specialised and likely to be few in any given country.

- requires robust feasibility with detailed patient population assessment
- requires development of strong site relationships and effective communications

As a global CRO, ICON has worked with almost every Tertiary Care Center where the specialists that see and treat patients with rare and orphan diseases are located.

ICON ensures that both sites and investigators have the right infrastructure and capabilities to conduct trials according to agreed-upon timelines.

In addition to its own integrated clinical site network in the US (PMG Research) ICON has partnerships with Site Management Organisations around the world. By implementing robust research infrastructures in large, multispecialty health systems, ICON unlocks access to millions of patients, streamlines the clinical trial process, and delivers on predictability and standardisation.

[ICONplc.com/sites](https://iconplc.com/sites)

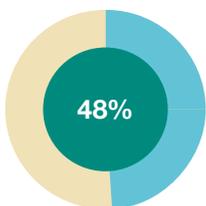
## Challenge 2: Designing and Evaluating Clinical Trials

Designing a rare disease clinical trial that can generate sufficient data, in addition to patient interest, is highly challenging.

Traditional study designs are not always appropriate since they are not an especially appealing option for individuals with rare diseases. Collaboration among clinicians, statisticians, and other well-qualified professionals is key to a strong study design and evidence-generation plan.

Identifying valid comparators within small patient populations is another difficulty, as standard of care varies from region to region, and often there are not effective treatments. For example, Canada will administer prophylaxis for adult and paediatric haemophilia patients. However, in Romania, only children will receive this particular treatment. Thus, there is not always a universal standard of care that can be used as a comparator in rare disease clinical trials.

These dual challenges – designing a trial that can meet enrolment goals and designating an appropriate comparator – make it difficult for orphan drug developers to gather sufficient data and build a compelling value story for their product.



Currently, 48% of orphan drug trials are placebo-controlled randomised controlled trials (RCTs)

## Solutions & Next Steps

### Choose the right clinical trial design

Achieving high-quality data in the orphan disease arena requires thoughtful study design. Given the difficult patient population and disease landscape, increasing trial complexity may impact quality and intensify burdens on paediatric investigators. Thus, simplicity is key to successful design for rare disease research. Patients may also be more inclined to participate if presented with the option of an open-label trial or a cross-over design, instead of a placebo-controlled RCT.

### Designate Appropriate Comparators

While identifying valid comparators is difficult, defining the most appropriate and compelling parameters requires extensive planning, as well as input from experts. Benchmarking treatment effects or demonstrating impact on patient health—using metrics such as fewer interactions with the health system, improved patient health status, and the overall survival rate of individuals who are taking a new drug—enables optimal evidence collection. Sponsors can also enhance their product’s chances of reimbursement by gathering these metrics during a clinical trial and juxtaposing them against results from current healthcare practices.

For instance, sickle cell anaemia patients will often receive blood transfusions. By analysing frequency of administration and the units of blood used, one can gauge how much these procedures are costing the healthcare system. If a patient’s participation in an orphan drug trial leads to fewer transfusions, developers can point to their product’s economic benefits for the market, thus strengthening the case for reimbursement.

## ADDPLAN

Adaptive design provides an opportunity for rare disease clinical trials, specifically to prevent underpowered studies; design seamless, multi-stage trials that protect patients; and enable effective reallocation of resources through early termination for futility or efficacy.

ICON’s ADDPLAN is a fully validated, regulatory-compliant software platform that helps sponsors design, simulate, and analyse adaptive clinical studies. Currently licensed by more than 50 pharmaceutical and medical device companies, as well as regulatory agencies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), ADDPLAN is central to ICON’s operational expertise and global experience in adaptive trials.

### Challenge 3: Ensuring the Quality of Patient Data

Measuring clinical trial outcomes is especially difficult when working with individuals who have rare diseases.

Due to the huge diversity in clinical presentation and patient experience, selecting an assessment strategy is a complicated process. Age, disease progression, and disease severity will influence reported outcomes, whether they be patient-reported outcomes (PROs), clinician-reported outcomes, or observer-reported outcomes.

Since many rare diseases impact young children and cause disabilities, patients could face significant challenges during self-assessment, such as reporting health status before and after diagnosis. Another challenge stems from response shift or individuals who accept their conditions as the “new normal”. When asked about the effects of their illness, they can no longer clearly gauge their level of burden. There are also individuals who can self-report, but only at the outset of a longitudinal study. Upon disease progression, they may no longer have the ability to provide a valid assessment or comparison of baseline. Thus, heterogeneity between rare disease patients adds many complications to data collection and clinical outcome assessment (COA) during a clinical trial.



EURORDIS represents the voice of rare disease patients in Europe.

ICON is proud to be a member of the EURORDIS Round Table of Companies (ERTC) which aims to facilitate exchange of ideas and common collaboration between member companies, government and regulatory authorities, academics and patients representatives.

[www.eurordis.org](http://www.eurordis.org)

### Solutions & Next Steps

#### Ensure data quality by engaging COA experts

Research studies can benefit from engaging Clinical Outcomes Assessment (COA) experts who understand the nuances of disease progression and PROs in rare diseases. They can provide the tools and knowledge needed to support the collection of valid data.

ICON can help sponsors find the most appropriate and valid Patient Reported Outcomes (PROs) to include in their orphan drug development. ICON's COA services are geared to meet the demands of global and national markets for high-quality, patient-centered data, and can assist sponsors with:

- COA endpoints and trial design
- Instrument selection, development, and validation
- Content validation
- Conceptual and endpoint model development
- Regulatory (e.g. FDA/EMA) support
- And much more



#### Value-based Healthcare and Patient Outcomes

ICON has been selected by the International Consortium for Health Outcomes Measurement (ICHOM) to help advance value-based care in rare disease and beyond through the launch of GLOBE, a worldwide healthcare outcomes benchmarking initiative. This programme will enable healthcare providers to compare high-quality, risk-adjusted outcomes and identify opportunities for improving their services. Drawing on 26 years of clinical and technical experience in data management, data analytics, and consultancy, ICON collaborates with ICHOM to accelerate the development of GLOBE.

[ICONplc.com/ichom](http://ICONplc.com/ichom)

## Challenge 4: Navigating Global Regulatory Requirements & Gathering Payer Evidence

As rare disease research often does not fit the traditional RCT mold, it is challenging to collect and communicate evidence that is compelling to regulators, let alone convincing to payers.

A firm understanding of how to navigate global regulatory environments is crucial to ensuring successful submission, especially in rare disease drug development. Because the definition of “orphan” changes from region to region, requirements for designation also vary. Below is a summary of the conditions a drug must fulfil in the US, the EU, and Japan.



### United States

In the US, orphan status is given to a drug that:

- Treats a disease that affects fewer than 200,000 people in the country

OR

- Is administered to fewer than 200,000 people per year (if the product is a vaccine, diagnostic, or preventative drug)

To qualify, a request for designation also must be submitted to the FDA Office of Orphan Product Designation with the information outlined in [21 CFR 316.20](#) and [316.21](#).



### Japan

In Japan, orphan status is given to a drug or device that:

- Is intended for use in less than 50,000 patients in the country
- Fulfils a vital medical need

Orphan designation applications should be submitted to the Ministry of Health, Labour, and Welfare. These will be evaluated in conjunction with the Japanese regulatory authority, the Pharmaceuticals and Medical Devices Agency.



### European Union

In the EU, orphan drug status is given to a drug that:

- Is intended for the treatment, prevention, or diagnosis of life-threatening or chronically debilitating diseases
- Treats diseases with a prevalence of no more than 5 cases/10,000 individuals
- Offers a significant benefit to individuals affected by a particular condition, especially if no other satisfactory methods of diagnosis, prevention, or treatment are authorised or existent

In Europe, applications for orphan designation are examined by the European Medicines Agency's Committee for Orphan Medicinal Products. The evaluation process will take a maximum of 90 days from validation. Requirements for regulatory submission can be found in the EU's, '[Guideline on the Format and Content of Applications for Designation as Orphan Medicinal Products and on the Transfer of Designations from One Sponsor to Another](#).'

	USA	European Union	Japan
<b>Scientific Advice</b>	Yes	Yes	Yes
<b>Marketing exclusivity</b>	7 years marketing exclusivity, if the drug is approved	10 years (+2 years for medicines with an agreed paediatric investigation plan)	Up to 10 years
<b>Financial assistance</b>	Reduction in fees and tax credits that amount to 50% of the cost of the trial	A waiver of marketing application user fees, which saves more than \$2 million	Reduction in fees and tax credits
<b>Grants</b>	Orphan Products Grants Programme	European Commission funding available	Government grants available
<b>Accelerated licensing procedure</b>	Fast Track Procedure	Centralised Procedure Conditional Approval	Priority Review Procedure

The granting of an orphan designation in any of the three regions does not alter the standard regulatory requirements.

## Solutions & Next Steps

### Generate data that not only fulfill regulatory requirements, but also resonate with payers

In addition to gaining a clear understanding of each region's regulatory requirements, drug developers also must be proactive about creating a compelling value story. Overcoming a regulatory hurdle does not necessarily correlate with a positive assessment from payers. For example, a drug for Morquio Syndrome was rejected by the Scottish Medicines Consortium because the data – captured from a 6-minute walking test – did not clearly demonstrate the true value that it provided to patients. Although the evidence collected was sufficient for regulatory approval, it left payers unconvinced. In order to successfully commercialise an orphan drug, drug developers must address factors that will become relevant at later stages of the product life-cycle, such as payer evidence.

### Real-World Intelligence

With ICON's Real-World Intelligence™ – real-world data (RWD) plus advanced expertise – developers will have the insights and tools to address key development challenges. ICON helps customers gain a deeper understanding of patient experiences and priorities, while accelerating market access for products that are truly aligned to payer and provider demands. ICON can provide sponsors with access to primary and secondary sources of RWD such as:

- Patient registries
- Electronic clinical outcomes
- Patient reported outcomes
- Apps & Sensors
- Electronic health records
- Integrated claims
- Syndicated research
- Social listening

[ICONplc.com/ehr-transformative](https://ICONplc.com/ehr-transformative)

## Reimbursement of Orphan Drugs

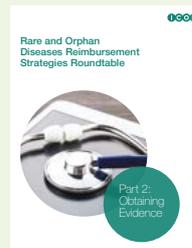
Is your orphan drug approved by regulators but still missing the necessary evidence to satisfy payers? Learn how to optimise your reimbursement and market access strategies with ICON's Rare and Orphan Disease Reimbursement Roundtable series.

Experts from ICON's Commercialisation & Outcomes services share key insights on three critical topics.



### Part 1: Identifying Evidence

Discover the lessons learned from years of orphan drug reimbursement experience, including strategies for addressing payer requirements and partnering with patient advocacy groups.



### Part 2: Obtaining Evidence

Find out how to gather appropriate evidence by looking beyond traditional clinical trials.



### Part 3: Communicating Evidence

Learn the importance of setting early expectations and strategies for successful evidence communications.

Access all three roundtable transcripts at [ICONplc.com/evidence](https://ICONplc.com/evidence)

## Therapeutic Experience

ICON is an experienced partner who can assist sponsors in navigating the many challenges of orphan drug development. ICON can help sponsors optimise the whole continuum of the clinical trial lifecycle from patient enrolment to payer reimbursement with its powerful solutions and proven strategies. Over the past 5 years, ICON's highly experienced clinical and therapeutic teams have conducted numerous rare disease trials across a wide range of therapeutic areas, including but not limited to:



202 rare disease studies



Over 25,167 patients



In 6,420 sites globally



Almost 250 staff with rare disease experience

Therapeutic Area	Indication
<b>Cardiovascular</b>	Amyloid Cardiomyopathy, Pulmonary Arterial Hypertension,
<b>CNS</b>	Amyotrophic Lateral Sclerosis, Angelman Syndrome, Cerebral Palsy, Chronic Inflammatory Demyelinating Polyneuropathy, Down Syndrome, Familial Amyloid Polyneuropathy, Friedreich's Ataxia, Huntington's Disease, Metachromatic Leukodystrophy, Neurogenic Orthostatic Hypotension, Progressive Supranuclear Palsy, Tinnitus, Traumatic Brain Injury, Transthyretin Mutations or TTR Amyloidosis
<b>Endocrinology</b>	Acromegaly, Growth Hormone Deficiency, Hypogonadism, Turner Syndrome
<b>Gastroenterology</b>	Crohn's Disease, Primary Biliary Cholangitis
<b>Genetic Disorder</b>	Hereditary Angioedema, Leber Congenital Amaurosis (LCA)
<b>Hematology</b>	Fabry Disease, Hemophilia A, Sickle Cell Disease
<b>Immunology</b>	Ankylosing Spondylitis, Dermatomyositis, Eosinophilic Asthma, Eosinophilic Esophagitis, Juvenile Idiopathic Arthritis, Kawasaki Disease, Multiple Sclerosis, Primary Immunodeficiency, Psoriasis, Sjögren's Syndrome
<b>Infection Disease</b>	Esophageal Candida, Invasive Aspergillosis
<b>Metabolic</b>	Progressive Familial Intrahepatic Cholestasis, Familial Hypercholesterolemia, Hunter Syndrome, Mucopolysaccharidosis, Phenylketonuria (PKU), Wilson's Disease
<b>Musculoskeletal &amp; Joint Disorders</b>	Osteogenesis Imperfecta, Polymyositis, X-Linked Hypophosphatemia (XLH), Fibrodysplasia Ossificans Progressiva, Limb Spasticity - Cerebral, Muscular Dystrophy
<b>Oncology</b>	Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Anaplastic Large Cell Lymphoma, Hodgkin Lymphoma, Basal Cell Carcinoma, Brain Cancer, Carcinoid Syndrome, Cutaneous T-Cell Lymphoma, Diffuse Large B-Cell Lymphoma, Esophageal Cancer, Follicular Lymphoma, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Chronic Lymphocytic Leukemia, Chronic Myeloid Leukemia, Lymphoblastic lymphoma, Mantle Cell Lymphoma, Mesothelioma, Multiple Myeloma, Myelofibrosis, Myeloproliferative Disorders, Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Ovarian, Pigmented Villonodular Synovitis Total, Refractory Follicular Lymphoma, Relapsed or Refractory CLL/SLL, Relapsed/Refractory Multiple Myeloma, Small Cell Lung Cancer, Soft Tissue Sarcoma, Symptomatic Carcinoid Syndrome
<b>Pulmonary and Respiratory</b>	Cystic Fibrosis, Idiopathic Pulmonary Fibrosis



**ICON plc Corporate Headquarters**

South County Business Park  
Leopardstown, Dublin 18  
Ireland

T: (IRL) +353 1 291 2000

T: (US) +1 215 616 3000

F: +353 1 247 6260

[info@ICONplc.com](mailto:info@ICONplc.com)

[ICONplc.com/rarediseases](http://ICONplc.com/rarediseases)