

Overcoming the Challenges of Rare Disease Drug Development



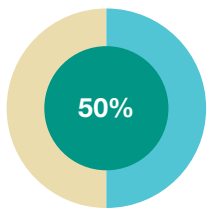
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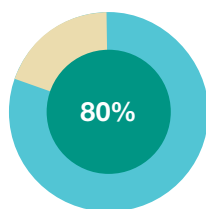
Overcoming the Challenges of Rare Disease Drug Development

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.

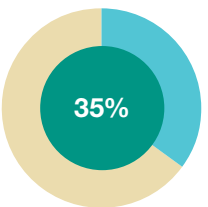
An estimated 350-400 million people worldwide suffer from rare diseases. Cumulatively, rare diseases are estimated to affect 1 in 17 people.



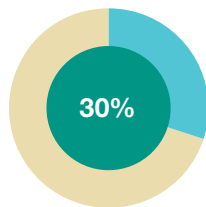
50% of rare diseases affect children



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 5th birthday

Orphan Drugs

Rare diseases without currently indicated treatments are called 'orphan' diseases and many countries have adopted specific orphan drug legislation to give incentives to develop drugs for these diseases. 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.

Orphan drug development

Successful orphan drug development requires a partner that can provide full strategic guidance and support across the treatment lifecycle including:

- Global regulatory strategy and operational execution
- Scientific leadership on rare disease treatment endpoint selection, development and validation
- Early drug development advice and guidance to optimise the pre-clinical profile
- Patient-based clinical trial designs that are scientifically robust and address the unique challenges of the disease
- Engagement and retention of patients in clinical trials, expanded access programs and patient registries
- Support for health care payer applications and negotiations to secure market access
- Communication with patients, health care providers and other disease community stakeholder groups to build support and advocacy for the development of new treatments

Challenge 1: Orphan Disease Designation and Regulatory Strategy

The development of an orphan drug involves two major independent steps: securing an ‘orphan’ designation for the target disease and conducting a robust pre-clinical and clinical research program tailored to the unique requirements of disease and the new therapy.

The initial key strategic consideration for a sponsor is an understanding of the disease definition and determining whether this will be granted an ‘orphan’ designation by regulatory authorities. Each major region with orphan drug legislation (US, EU, Japan) has a different interpretation and approach. The major orphan disease definitions and differences between regions are outlined here:



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)



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
- Fulfills a vital medical need

Solutions

Obtain regulatory and epidemiologic guidance

By working with regulatory and epidemiologic experts with experience in each region, sponsors can ensure success at this initial stage.

It is critical to understand ways to optimise incentives offered in each region, how to meet current regulatory standards and ways to ensure that novel aspects of the development program such as endpoint, patient selection, and treatment modality are well understood and validated by regulatory authorities.



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

The next major strategic regulatory consideration is the proposal of a robust development program. Drug development for orphan drugs requires different approaches due to small patient populations and the complex pathology of these illnesses. In addition, many innovative therapies such as gene therapies, are being developed for these diseases.

The adjacent table describes the major incentives offered for orphan drugs in each region.

	USA	European Union	Japan
Scientific Advice	Yes	Yes	Yes
Marketing exclusivity	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
Financial assistance	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
Grants	Orphan Products Grants Programme	European Commission funding available	Government grants available
Accelerated licensing procedure	Fast Track Procedure	Centralised Procedure Conditional Approval	Priority Review Procedure

Challenge 2: Optimal Pre-Clinical and Early Drug Development to Ensure Trial Success

The complex pathology of rare diseases and the small patient populations associated with rare diseases means that pre-clinical and early drug development need to be rigorously designed.

Key elements in pre-clinical development for orphan medications are:

- Rigorously designed preclinical models
- Establishing target engagement
- Non-human primate studies
- Biomarkers and PK/ PD modeling
- Chemistry, Manufacturing & Controls (CMC).

In addition, early clinical development for rare disease is fundamentally different because it involves testing of the drug directly on patients. As a result there are unique challenges that need to be considered such as:

- Legal requirements for first in human studies in patients and children
- Logistics of patient access to Phase 1 clinics
- Optimal treatment designs for Phase 0 (proof of concept) and design combining Phase 1 and Phase 2a data collection activities
- Efficiently pairing early phase Clinical Pharmacology and Safety expertise with therapeutic expertise
- Maximizing efficiency in transitioning from safety testing in Phase 1 to efficacy in Phase 2
- Analyzing safety data efficiently to identify trends and outliers early (i.e. Data Visualization), so as to minimize risk for the limited patients involved in rare disease studies

Solutions and Next Steps

Obtain guidance on pre-clinical, manufacturing and drug development strategies

ICON maintains a world-renowned team of pre-clinical, manufacturing and drug development experts to provide comprehensive guidance on strategies for orphan drugs.



Challenge 3: Selection of Appropriate Treatment Outcomes

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.

Solutions & Next Steps

Ensure data quality by engaging COA experts

Research studies can benefit from engaging 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 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:

- Trial endpoint strategy and design support
- Instrument selection, development, and validation
- Full language services (language and cultural validation)
- Regulatory filing and negotiation support



Mapi Research Trust is a non-profit organisation dedicated to improving patients’ quality of life by facilitating access to Patient-Centered Outcome (PCO) information.

Through the Trust, ICON has access to world-leading experts as well as Clinical Outcome Assessment (COA) developers and authors with unique insights in overcoming scientific barriers.



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](https://iconplc.com/ichom)

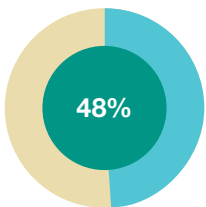
Challenge 4: Designing and Evaluating Clinical Trials

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 products 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.

[ICONplc.com/addplan](https://www.ICONplc.com/addplan)

Challenge 5: 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.

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 (EURORDIS). EURORDIS, 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.



ICON is a proud member of NORD which is committed to providing services for patients and their families, rare disease patient organizations, medical professionals and those seeking to develop new diagnostics and treatments.

www.rarediseases.org



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

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.

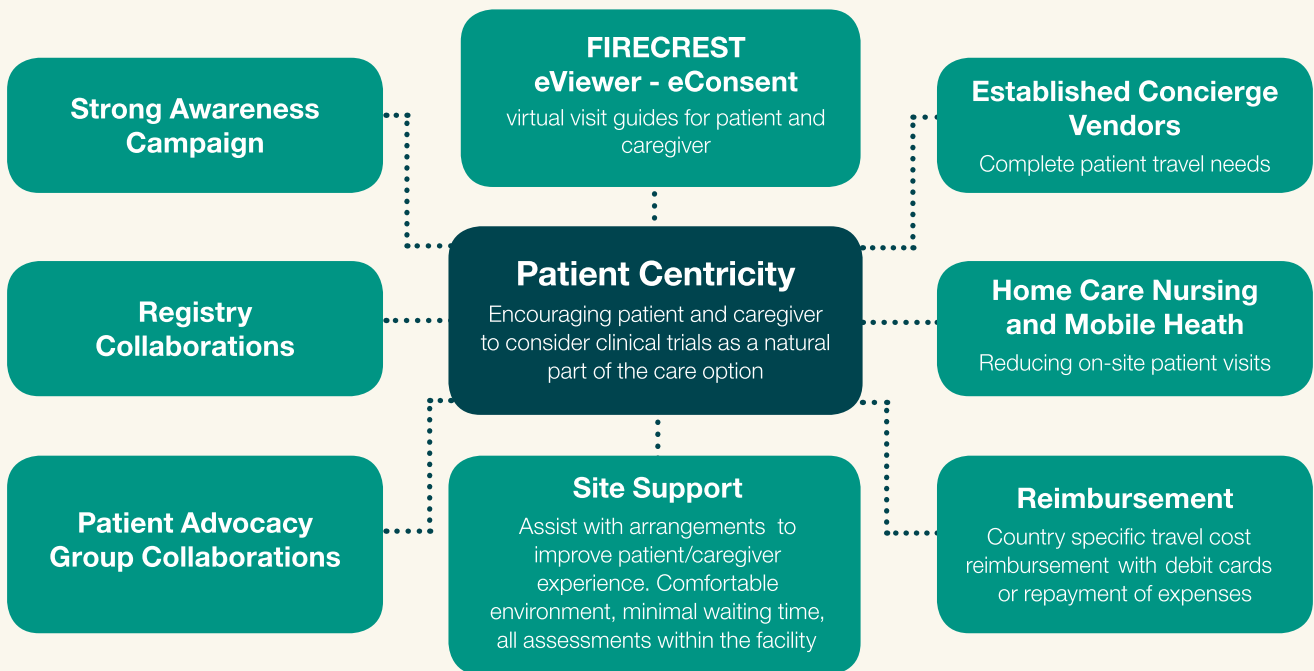
ICON has a Patient Recruitment Solutions (PRS) team to ensure targeted patient recruitment timelines are met.

ICON's Patient Enrolment and Retention Manager together with the Project Manager will develop the study level recruitment plan, and support the Clinical Research Associates in developing site specific recruitment plans thereby addressing any gaps and ensuring each site is able to fulfill their enrolment objectives within the agreed timelines.

PRS strategies and tactics will be defined and adjusted to each site after the Pre SV study visit (PSV).

- Concierge/Travel Services, Home Health Visits
- Engagement of site social workers, advocacy groups and community resources Instrument selection, development, and validation
- The ICON innovation group can assist in identification, selection, development and implementation of COAs and technology such as wearables, remote monitoring, sensors and virtual visits

Built for Purpose Patient Centric Solution



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



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, 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



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

FIRECREST

FIRECREST digital solutions increase efficiency in clinical trials by driving site performance and enhancing patient engagement. It is deployed across 1,400 studies in 100+ indications, with over 500,000 registered users, including the top 10 global pharmaceutical companies.

Solutions include;

- Site Portal
- Training Site & Study Staff
- Visit by Visit Guide
- eDocument distribution and
- Pre-Screen
- eConsent

FIRECREST 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/FIRECREST

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.

ICON is a market leader in all disciplines needed to commercialise orphan drugs and manage rare disease programs.

Real World Evidence: Industry leaders in real world research to support regulatory requirements, commercialisation evidence, and engage treatment populations

Patient Insights and Engagement: Services to increase recruitment and retention, develop relationships with patient advocacy groups and ensure the patient's voice is heard throughout the lifecycle of drug discovery, from protocol development to post marketing

Patient-Reported Outcomes: World-renowned leadership with access to over 4,000 PRO measures and expertise in custom scale development

Language Services: Recognized leaders in linguistic validation, patient support, and HCP materials

Strategic Regulatory Services: Offering consultation and experienced procurators for regulatory meetings.

Pharmacovigilance & Risk Management: Experts in international pharmacovigilance and safety, with strategically placed qualified PV contacts.

Real World Evidence Strategy & Analytics: Global health economics team with expertise in rare disease research, including meta-analysis, cost consequent analysis, and market access to support payers and health technology assessments

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

Reimbursement of Orphan Drugs

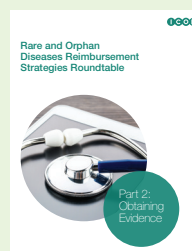
Is your orphan drug approved by regulators but still missing the necessary evidence to satisfy payers? Learn how to optimise your reimbursement and market access strategies with ICON's Rare and Orphan Disease Reimbursement Roundtable series.

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 10 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:



252 rare disease studies



Over 36,000+ patients



In 9,000+ sites globally



Almost 290 staff with rare disease experience

Therapeutic Area	Indication
Cardiovascular	Amyloid Cardiomyopathy, Pulmonary Arterial Hypertension, Hereditary Angioedema
Central Nervous System	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
Endocrinology	Acromegaly, Growth Hormone Deficiency, Hypogonadism, Turner Syndrome
Dermatological System	Psoriatic Arthritis
Ophthalmology	Retinitis Pigmentosa, Leber Congenital Amaurosis (LCA)
Musculoskeletal & Joint Disorders	Osteogenesis Imperfecta, Polymyositis, X-Linked Hypophosphatemia (XLH), Fibrodysplasia Ossificans Progressiva, Limb Spasticity - Cerebral, Muscular Dystrophy
Metabolic	Progressive Familial Intrahepatic Cholestasis, Familial Hypercholesterolemia, Hunter Syndrome, Mucopolysaccharidosis, Phenylketonuria (PKU), Wilson's
Hematology	Fabry Disease, Hemophilia A, Sickle Cell Disease, Thalassemia
Immunology	Ankylosing Spondylitis, Dermatomyositis, Eosinophilic Asthma, Eosinophilic Esophagitis, Juvenile Idiopathic Arthritis, Kawasaki Disease, Lupus, Multiple Sclerosis, Primary Immunodeficiency, Psoriasis, Sjögren's Syndrome
Gastroenterology	Crohn's Disease, Primary Biliary Cholangitis
Pulmonary and Respiratory	Cystic Fibrosis, Idiopathic Pulmonary Fibrosis
Infection Disease	Esophageal Candida, Invasive Aspergillosis
Oncology	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, Non-Small Cell Lung Cancer, 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, Thalassemia
Ophthalmology	Retinitis Pigmentosa



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About ICON

ICON plc is a global provider of outsourced development solutions and services to the pharmaceutical, biotechnology and medical device industries. The company specialises in the strategic development, management and analysis of programmes that support clinical development. With headquarters in Dublin, Ireland, ICON currently operates from 87 locations in 38 countries and has approximately 13,250 employees. Further information is available at [ICONplc.com](https://www.iconplc.com).