Rare Disease

Uncommon Skills for Special Challenges

Building a pharmaceutical development program for the treatment of a rare disease is a monumental task. You know the challenges: poor understanding of the natural history due to few investigators studying the disease, heterogeneous patient populations with variable phenotypes and clinical courses, geographic dispersion of patients and investigators, regulatory uncertainties, and lack of prior clinical studies to establish a template for study execution. In addition, small patient populations challenge traditional methods of study operation. With >7000 rare diseases, each exhibiting diverse symptomatology, the key is *expertise* rather than disease-specific experience. You need a CRO with **proficiency in these core functions:**

- Accessing small populations and pediatric populations
- Assuring site competency in the targeted indication
- Confirming and facilitating site GCP adherence
- Exploiting innovative, efficient study designs
- Implementing "participatory" research models
- Managing supportive-care endpoints, especially neuropsychiatric and patient-reported outcomes
- Minimizing subject and caregiver burden
- Submitting INDs for novel or repurposed products

Worldwide Clinical Trials (WCT) delivers this expertise. Our scientific, medical, operational, and regulatory staff contribute unique skills with finesse to meet the special demands of rare diseases.

Foundational Goals: Recruitment & Retention

In rare-disease trials, the need to recruit and retain patients influences every decision. The protocol must account for the vulnerability of the patient population and address ethical considerations, particularly if the study design mandates discontinuation of therapy considered essential for patient support. Eligibility criteria influence the number of available subjects, as well as the likelihood of establishing a database from which evidence of efficacy and safety can be deduced for a more generalized population.

The frequency of visits and number of assessments impact patient and caregiver burden and compliance. WCT may recommend in-home nurse visits for some procedures when patient mobility is likely to be a problem and financial and logistical aid for travel and lodging. Patient associations provide an advisory role during protocol drafting, specifically regarding feasibility of requested procedures in relation to possible patient and caregiver inconvenience.

Rare diseases exert a substantial physical, emotional, and financial impact on patients and loved ones. Rendering the diagnosis is often difficult. Many rare diseases are fatal in infancy or childhood. Children who survive to adulthood face difficulties transitioning from pediatric to adolescent to adult care, and clinical presentation will evolve. Further, treatment often involves multiple specialties such as neurology, gastroenterology, psychiatry, endocrinology, and physical therapy because comorbidities are common. WCT considers all of these factors when creating the study plan and obtains input from key opinion leaders (KOLs) on diagnostics, outcome measures, and care processes.

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GCP=Good Clinical Practice, IND=Investigational New Drug Application

RARE DISEASE PORTFOLIO

- Acromegaly
- Amyotrophic lateral sclerosis
- Cystic fibrosis
- Duchenne muscular dystrophy
- Down syndrome
- Fabry disease
- Frontotemporal dementia
- Gaucher's disease
- Growth hormone insensitivity syndrome
- Hemophagocytic lymphohistiocytosis
- Idiopathic pulmonary fibrosis
- Idiopathic thrombocytopenic purpura
- Juvenile idiopathic arthritis
- Lambert-Eaton myasthenic syndrome
- Mucopolysaccharidosis I (Hurler syndrome)
- Mucopolysaccharidosis II (Hunter syndrome)
- Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
- Niemann–Pick disease type C
- Sickle cell disease
- Thrombotic microangiopathy
- Von Willebrand disease
- Velocardiofacial syndrome, psychosis

Country and Site Feasibility

Finding and activating qualified sites is among the most difficult tasks in rare-disease trials. Country selection involves: (1) identifying countries with a sufficient number of potential study participants, (2) determining whether these patients are accessible; and (3) identifying centers of excellence with the therapeutic and operational capabilities to execute the trial. WCT considers the medical, cultural, and regulatory context as well as the standard of care and treatment pathways within each country of interest.

Our experience working with pediatric hospitals and research networks, specialized treatment centers, and academic institutions benefits your program. We connect with patient organizations and enlist KOLs internationally to assist in site identification and patient recruitment. When internal rather than centralized Institutional Review Boards and Ethics Committees are mandatory, WCT can assist with obtaining approvals and negotiating contracts to yield more predictable timelines.

If there is no patient advocacy group, identifying and locating patients can be extremely challenging. General registries (eg, Global Rare Disease Patient Registry and Data Repository[a]); entities such as the National Organization for Rare Disorders and the European Organisation for Rare Diseases; and resources such as Orphanet[b] are invaluable in this regard.

Once sites are selected, WCT conducts site-by-site recruitment and retention analysis and planning and undertakes specialized outreach. When studying a rare disease, every single patient's participation is vitally important. WCT engages sites, investigators, and patients to confirm acceptance of the study design. You can rely on us for compelling patient educational materials, advocacy websites, and other persuasive campaigns to motivate participants.

Recruitment and retention benefit from WCT's implementation of "participatory" research, proactively engaging all stakeholders—including patients, caregivers, scientists, clinicians, and communities—to foster a collaborative approach. An expanded access/compassionate use program that complements an interventional orphan-drug trial facilitates recruitment, retention, and commercial value.

Pediatric Research

Approximately 50% of patients with rare diseases are children. Their continual growth, developing attitudes and beliefs, and unique perceptions, as well as family dynamics, all factor into recruitment and retention. A pediatric rare-disease study might only enroll 1 to 3 patients per year per site. Therefore creative, proactive plans are mandatory, with a careful balance between minimizing risk and discomfort and obtaining meaningful data. Patient assent to participation should be obtained via age-appropriate communications. Rescue medications and open-label extensions can facilitate parental, ethical commission, and regulatory approvals. Informed safety monitoring must be scheduled to minimize disruptions to family and school activities.

[a] Launched in 2012 by US National Institutes of Health Office of Rare Diseases Research.
[b] Orphanet, led by a consortium of 40 countries, is a reference portal for information on rare diseases and orphan drugs, for all audiences.
[c] WCT partners with a range of specialized service providers, including centralized clinical and imaging laboratories, drug procurement and management specialists, and logistics support for transfer of temperature-controlled pharmacokinetic samples, etc. The WCT Bioanalytical Sciences Lab also has the capability of handling samples and transferring in methods for bioanalysis.

Rare Disease

KEY SERVICES

- Biostatistical analysis
- Clinical monitoring
- Data management
- Data and Safety Monitoring Board charters and management
- Drug depot services
- Electronic data capture
- Endpoint adjudication
- Global project management
- Investigator meetings
- Medical monitoring
- Medical writing
- Pharmacovigilance
- Protocol design and feasibility assessment
- Quality assurance
- Rater training
- Regulatory affairs (includes consultancy)
- Safety monitoring
- Scientific consultancy
- Site identification, recruitment, and management
- Supply management and randomization
- Third-party collaboration for specialized assessments[c]
- Trial master file

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WWCTRIALS.COM

WORLDWIDE CLINICAL TRIALS
SCIENTIFICALLY MINDED • MEDICALLY DRIVEN

Meeting Trial-Design Challenges

WCT offers state-of-the-art trial design capabilities to maximize valuable patient data and reduce developmental timelines for trials with small, geographically dispersed sample sizes. Possibilities include:

- Normal volunteers, patients, and hybrids for first-in-human studies
- Single ascending dose/multiple ascending dose permutations
- Crossover and Latin square designs
- Enrichment designs (compliance, safety, efficacy)
- Delayed start designs/randomized withdrawals
- Group sequential designs
- Sample size re-estimation procedures
- Adaptive dose-finding (Bayesian or frequentist)
- Adaptive hypotheses (superiority to non-inferiority)
- Concurrent observational studies and post-approval registries

WCT Is Your Regulatory Ambassador

Securing regulatory approval for the designs often required in rare-disease trials can be difficult. Our scientific and regulatory professionals have experience interacting with authorities to advance programs in rare indications. WCT surpasses the usual consultative role and, if necessary, will present to the FDA in person to make your case; for example, defending limitations in nonclinical data or use of non-validated biomarkers that are "fit for purpose," or recommending innovative trial designs for proof of principle.

An example of how WCT champions your program may be found in the FDA decision to create a new indication for a monogenetic orphan disease with 180 phenotypes. An IND for a repurposed product was rejected by the FDA for the following reasons: insufficient natural history (common in many orphan indications); preclinical data obtained before the advent of Good Laboratory Practice Guidelines; limited safety data; and inadequate toxicology supporting exposure duration. WCT successfully argued for the relevance of prior human studies in other indications, the interplay of genetic/clinical phenotype as it would inform a program of prudent clinical research, and the appropriateness of demonstrating proof of concept prior to replication of preclinical data. The resubmitted IND was accepted, and the discussions helped prompt the development of the new indication.

Partner with us for strategic therapy development.

Related Link:
Rare Diseases: Common Issues in Drug Development Guidance for Industry
August 2015 FDA Guidance

CAT=Clinical Assessment Technologies

Rare Disease

INTEGRATED TECHNOLOGY

- Clinical Trial Management System
- Electronic Data Capture
- Interactive Voice Response System (IVRS)
- Interactive Web Response System (IWRS)

WCT's Supply Management and Randomization Technology (SMaRT) offers a cost-effective solution for centralized randomization, drug inventory management, and controlled code-break capabilities. We also develop bespoke solutions for sponsors. With the capability to integrate complex needs into sponsor data systems, we can reduce costs while enhancing both quality and efficiency.

CLINICAL ASSESSMENT TECHNOLOGIES™

Accurately predicting site performance and GCP compliance is especially difficult in rare-disease indications. CAT oversees the integrity and clinical meaningfulness of your program's assessments. Features include:

- Corroboration of patient eligibility
- Custom-designed CAT plan to ensure consistent calibration of assessments
- Practical standards for rater credentials and certification
- Rigorous rater training
- Meticulous in-study data surveillance
- Database build monitoring
- Scale and translation management

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