Worldwide Clinical Trials

Rare Disease Playbook

I. Why Worldwide

You started out hoping to make a difference in the world. You put time, effort, and a lot of heart into your product to bring it this far. You deserve to work with a CRO who not only understands that on a very personal level — but one who is going to care as much as you do. At Worldwide Clinical Trials, we have not lost sight of why we started out, either. We want to make a difference, too.

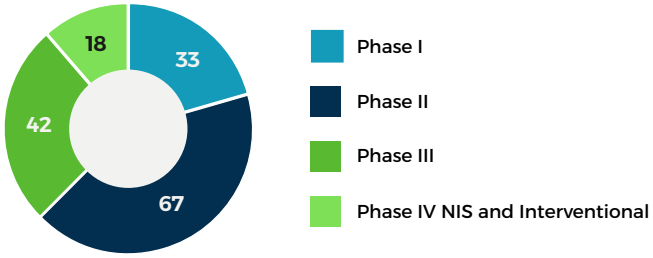
You deserve a CRO who walks alongside you with equal passion — but one with the experience, expertise, and trust to "give it to you straight," too, if the situation calls for it. That's because we're as invested in your study as you are. It matters to us. You're never going to be "just another study" here — at Worldwide, you'll get hands-on attention from our senior staff; a nimble, customized solution; and the assurance that our hearts are in this as much as yours.

Here at Worldwide, each person on your project team has chosen to pursue a career in rare disease clinical research, and the passion they bring to their work is what makes Worldwide different. They are accessible, reliable, and flexible — because they know they are a key part of advancing your compound toward patients who need it.

Specializing in Rare Diseases in:

- Oncology
- Neuroscience
- Metabolic
- Respiratory
- Hematology
- Nephrology

Experience by Phase



160+ Trials

4,610+ Sites

75+ Investigators

55+ Countries

19,000+ Participants

Our Approach

We know there's no one "out of the box" solution or path to study success. That's why we take an approach that involves optimal strategic decision-making in the development stage of a novel drug.

Identifying Objectives
Clearly defining the goals and desired outcomes of the project or program

Adaptive Planning
Implementing flexible strategies that can be adjusted as needed in response to changing conditions or emerging challenges

Resource Allocation
Optimizing the use of resources to maximize efficiency and effectiveness

Stakeholder Collaboration
Engaging with all stakeholders, such as clients, regulatory authorities, patients, and advocacy groups to ensure a coordinated and inclusive approach

Performance Monitoring
Continuously tracking progress, assessing results, and adjusting strategies to drive ongoing improvement and success

Being strategically focused means more than successful execution of a single trial. Working together, we focus on your longer-term needs beyond an individual study, envisioning the scope and detail of your full development program. We're invested in your success, partnering with you throughout your entire program.

Featured

A Rare Disease Partnership that Grows with You

Our sponsor came to us in 2013 needing bioanalytical services for a sickle cell disease (SCD) study. In 2015, we began providing late phase services, and since then we have provided development services for 10 studies across all phases and two programs.

These studies have taken place on a global footprint and in all age groups, from three-month old infants to adults. The primary program we supported secured the data necessary to receive approval in adults and pediatric populations.

Today, our partnership continues even after their acquisition. We've developed a dedicated team for this sponsor to ensure consistent training and best practices across all their studies.

We believe in creating partnerships that last beyond a study.

Bringing Treatments to Patients Together

2013
Partnership begins with early phase work on product for SCD

2015
Awarded Phase II international study on product for idiopathic pulmonary fibrosis (IPF)

Awarded international Phase II study on product for SCD

2016
Awarded Phase II international study on product for SCD

Awarded Phase II US-based study on product for IPF

2019
Sponsor receives accelerated FDA approval on product ;patients 12 years and older with SCD. Worldwide developed and validated 17 total methods and analyzed samples in 35 studies

Awarded Phase II international pediatric study on product for SCD

2020
Awarded Phase IV international adolescent and adult study on product for SCD

Awarded Phase IV international pediatric study on product for SCD

Awarded Phase IV international study on product for SCD

2021
Awarded Phase IV international adolescent and adult study on product for SCD

Awarded a rescue Phase III international pediatric study on product for SCD

FDA approves use of product for SCD in children over the age of four

2022
Sponsor is acquired for $5.4 billion by a top 5 pharmaceutical company

Early Engagement

As part of our commitment to innovative study and program design, one of our founders established a team of translational research scientists adept in clinical research methodology to provide early engagement consultation to assist with:

- Pre-IND/Pre-CTA meetings
- Portfolio reviews to help determine the most appropriate indication for the asset
- Clinical development plans
- Orphan drug designation applications
- Fast track and breakthrough therapy designation requests
- Study design

II. Biomarkers, Novel Endpoints, and Inter-rater Reliability in Rare Disease Research

At Worldwide, we have some of the most sensitive assays for rare disease biomarkers, capable of accurately measuring the up/down regulation of endogenous neurotransmitters in plasma and cerebrospinal fluid (CSF). We also support the measurement of low levels of steroids using novel approaches of derivatization and LC-MS/MS analysis. We are and will continue to remain at the forefront of regulations, adding to our existing panel of biomarkers as they become available.

When applicable, we use insights from ongoing patient and clinical KOL consultations to create sensitive, custom outcome measures and study endpoints which not only clinically demonstrate your product's efficacy but also track a meaningful change in symptoms or quality of life from the patient and family perspective.

We develop fit-for-purpose outcomes and endpoints by:

- Using clinical experts to unite the patient experience with clinical and scientific feasibility
- Pilot testing and formally validating our metrics
- Working with the FDA frankly and frequently
- Documenting every step and decision to support regulatory acceptance
- Keeping in touch with all relevant stakeholders throughout the process

5 Key Points About Biomarkers

- Rare diseases are often poorly understood and can have limited biomarkers available.
- Biomarkers can be valuable in diagnosing and monitoring rare diseases, as well as helping researchers understand their underlying biology.
- Biomarkers can help identify patients with similar disease characteristics and track disease progression over time.
- Biomarkers can aid in the development of diagnostic tests and help assess the efficacy of new drugs in clinical trials.
- Developing biomarkers for rare diseases can be a challenge, but advances in technology and knowledge are enhancing their discovery and use in clinical research.

Rater Training

Our robust rater training approaches aim to minimize variability, improve inter-rater reliability, and reduce noise by considering the following when developing a customized training program for your study:

- The number and order of assessments in a given visit
- Specific considerations when using the chosen measures with the identified population
- How the assessments are to be used in the trial
- Potential site, patient, and caregiver burden
- The experience level of each rater with the targeted indication, population, and study measures and how that can impact their evaluation of symptoms, performance, and overall patient well-being
- The level of research experience vs. clinical care experience among raters
- The homogeneity of raters
- Previous training certifications
- Experience with key study measures and the frequency of administration in recent years
- Any scale holder/licenser requirements

Our inhouse clinical and operational expertise, with hundreds of trial assessments, has been instrumental in reducing variability, noise, and placebo response that often plague clinical trials (particularly in rare disease trials), in turn boosting the credibility of our sponsors' studies and their findings.

III. Overcoming Patient Recruitment and Retention Hurdles

Identifying Patients

With the geographical dispersion of many rare disease populations, it can be difficult to locate patients and obtain the participation needed for rigorous data collection. We start with your disease and your patients, looking to understand at a deep level what it truly means to be a patient with that disease and how it could impact their desire to enroll and stay in your trial.

Our strategic teams explore options for making participation easier and increasing the diversity of patients. We start with your study, your patient, and your unique team, and leverage our extensive lessons learned to drive recruitment success through methods such as:

- Employing cross-border enrollment for global recruitment
- Incorporating elements of decentralized clinical trials
- Leveraging unique recruitment methods to meet the patient where they are
- Accounting for the existing standard of care and current competitive trial landscape
- Accommodating the patient's everyday lifestyle
- Evaluating the flexibility of exclusion criteria
- Considering the caregiver's part in participation

Recruiting & Retaining Rare Disease Patients

Rare disease trials often require specialized recruitment and retention strategies that take into account the unique attributes of the trial's stakeholders. We have successfully delivered diverse rare disease programs with varying patient populations and disease-related influences. Knowing every study is unique, we use the knowledge we have from our extensive prior experience to determine the best recruitment and retention approach for your specific study.

We also factor in the need to be flexible. Recruitment challenges are one of the biggest hurdles trials face, and preparing a backup plan or being able to pivot quickly when challenges arise is a key part of providing excellent clinical development services. And, we continuously explore innovative ways to support recruitment and retention by building partnerships with new vendors, working with patient and the advocacy communities, and working with others in our industry with similar missions.

Strategies for Rare Disease Patient Identification

Pathway is known

Snowball technique

- Refer to literature and experience for KOLs in indication

Hub and spoke

- KOLs at university hospitals have referral networks that can support recruitment

Registries and advocacy group involvement

Patient insight networks—access to registry information

Prescreening protocol

Family histories

Pathway is Unknown

In isolation, signs and symptoms mean nothing, and clustering of signs and symptoms do not necessarily equal diagnosis.

Leverage data vendors, allowing for patient outreach through physician:

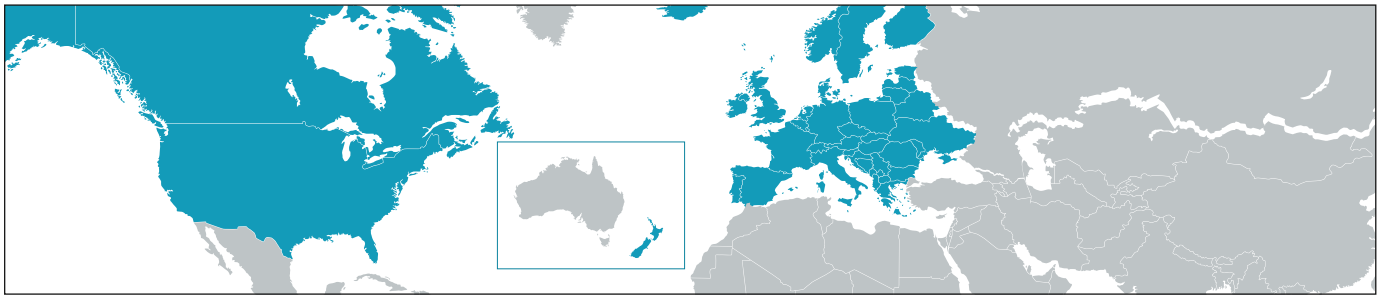
- Access to large databases of information: DOD, Medicare Services, etc.
- Aggregate data using algorithm determined by medical team (data mining)

IV. Incorporating the Patient Experience

Engaging with Global Advocacy

Successful studies require a CRO who has not only considered but truly embedded the patient's insight and perspective into the center of the trial design. Personally and professionally, our Rare Disease Strategy Leads are invested in advancing the priorities of rare disease advocacy organizations and making treatment options available to the rare disease community through enrollment partnerships. Our teams have built mutually beneficial relationships with **more than 60 patient advocacy organizations across the world,** advancing their agendas and enrolling trials for our sponsors.

Global Reach of Our Partnerships



Therapeutic Areas

Autoimmune	Hepatology	Metabolic	Neurology	Pediatric	Rheumatology
Hematology	Infectious Diseases	Nephrology	Ophthalmology	Respiratory	Umbrella Organization

When studies are designed with patients in mind, studies recruit and retain the patients they need, and if approved, enter the market with patient and physician support. It is this type of collaboration we believe will make clinical trials better for everyone.

Integrating the Patient Voice

We frequently offer patient advocate and caregiver consultants a seat at the table in discussions with our sponsors, and we consult advocacy organization feedback for diverse insights on protocols, patient support materials, and recruitment strategies. This patient involvement leads to better recruitment and retention outcomes and ultimately the success of your trial.

Before the Trial

- In person or virtual patient focus groups, patient insights panels, and patient advisory panels
- Patient education surveys

During the Trial

- Interactive, educational videos
- Patient-focused annual updates
- Patient and caregiver satisfaction surveys

After the Trial

- Clinical trial transparency
- Lay language summaries

Why We Are Committed

Trials that work for patients, work for sponsors. When we can, we engage with our sponsors early to help ensure from the start that the trial will be a success.

When we are brought in early, we can help sponsors consider:

- What potential lifestyle challenges could prevent a patient from enrolling or participating for the duration of the trial?
- Does this compound treat the symptoms the patient is most concerned with?
- Does the formula make sense for the age, physical limitations, and lifestyle of the patient?
- Is the protocol feasible for this patient population and their potential caregivers?

V. Cell & Gene Therapies

Therapeutic Areas of Expertise:

- Hematology
- Infectious Disease
- Metabolic
- Cardiovascular
- Neurology
- Oncology
- Opthalmology

Treatment Modalities:

- Autologous Hematopoietic Stem Cells
- Autologous Mesenchymal Bone Marrow Stromal Cells
- Chimeric Antigen Receptor T-Cells (CAR T)
- Adeno-Associated Virus (AAV)-Vectored In Vivo Gene Therapy
- Antisense Oligonucleotides (ASO)
- miRNA

At Worldwide Clinical Trials, we have a legacy and continued focus in helping to design complex programs like cell and gene therapies, successfully — scientifically, regulatorily, and operationally. We are set apart by our passion for partnership, innovation, and excellence, as we advance these treatments for our sponsors and bring meaningful treatments one step closer to patients.

Our cell and gene therapy strategic and scientific leads have:

10+ average years of experience with CGT trials

160+ CGT studies supported

40+ CGT publications & presentations

Cellular & Genetic Medicines Experience

Pediatric & Adult

Phases I - IV

Rare & Non-Rare Indications

Involving Key Stakeholders

Our dedicated teams are well versed in the nuances of cell and gene therapy studies and aligning development programs to the needs of patient communities. We take a disease- and modality-specific strategic approach to your program, approaching every trial as a unique opportunity to bring forward life-changing therapies and improve patient outcomes.

Further, our Clinical Research Methodology fellows provides consultatory and early engagement support for drug development programs. They remain current on the latest research, regulatory changes, and lessons learned that emerge within cell and gene therapy to leverage their insights in real-time into the programs we currently support.

VI. Diversity Considerations for Rare Disease Trials

In April 2022, the Food and Drug Administration (FDA) issued draft guidance on developing a "Race and Ethnicity Diversity Plan" for clinical trials. The guidance is designed to help make clinical trial enrollment more representative, supporting diversity, equity, and inclusion (DEI) initiatives. Late in 2022, the Food and Drug Omnibus Reform Act (FDORA) was enacted. The legislation requires that diversity action plans (DAPs) be submitted, tasking the FDA with issuing guidance on the specifics of what to include in a DAP, including:

Pilot testing and formally validating our metrics

The age group(s), sex, race, and ethnicities to be addressed by the plan

How the sponsor should modify or update the plan and let FDA know about progress

Considerations for sponsors to post key information about their DAPs for the public

Criteria the agency will use when it considers granting a waiver from DAP requirements.

The provisions of this yet-to-be-issued guidance will align with the existing draft guidance on Diversity Plans; this space is rapidly moving.

For rare disease trials — which are already challenging to enroll — the guidance and requirements for Diversity Plans deserve special focus, because it's "rarifying" an already rare disease by expanding into rare subtypes of a disease. The FDA recognized the difficulty in recruiting for rare diseases, encouraging sponsors to become more resourceful and intentional about trial enrollment and retaining patients.

Considerations For Addressing Diverse Enrollment

- Enroll international sites. Expanding abroad could help sponsors recruit more ethnicities within certain populations while also increasing treatment access to more people.
- Work to overcome access barriers in the United States.
- Employ a human- and community-first approach powered by focus groups staked on listening, learning, and acting.

VII. Successful Project Management of Rare Disease Studies

A clinical trial requires coordination of multiple stakeholders within the trial itself, as well as alignment with various regulatory bodies. A study team that lacks clearly articulated roles and accountabilities runs a high risk of timeline or budget inflation and could even render unreliable data. At Worldwide, our project management team focuses on role clarity and ensuring sites are operating in alignment with study protocols and regulatory requirements.

The most efficient strategic relationships result in a matrix of engagements, where individuals possessing different subject matter expertise remain for the duration of a program, with varying levels of contribution throughout the program's evolution. At Worldwide, we dedicate experienced — not junior — medical, scientific, and operational staff to every rare disease study.

No matter the disease or the therapy, there are always questions about how best to operationalize a study to meet patient, family, caregiver, sponsor, and regulatory requirements. These questions can be even more difficult when the disease presents with a complex phenotype, such as an orphan disease. There may be limited study experience in support of the disease in question — thus fewer guideposts in terms of the design and operational insights from prior studies, regulatory interactions, and the eventual commercialization of a novel therapy. Yet within orphan disease clinical research, the nature of the development program demands preemptive risk mitigation and planning, fulfilling the requirements of the FDA's Accelerated Development program, which is expressly intended to speed up the development process for these indications. At Worldwide, our experts are always accessible to you throughout the entire study.

The ideal interaction between a sponsor and CRO involves multiple interactive activities that empower all parties to become versed in the relevant business, regulatory, and clinical issues.

VIII. Real-World Evidence in Rare Disease Research

At Worldwide Clinical Trials, we are experienced in the design and execution of rare disease research initiatives that embrace the evolving need for real-world evidence at all points along the drug development and commercialization lifecycle.

- Our dedicated evidence team supports the development and implementation of health economics and outcomes research, observational studies and patient registries, and patient communities in key orphan diseases.
- Strategically combining prospective research with innovative data sources, we balance the needs of clinical development with marketplace realities demanding communication of real-world evidence with clinical, economic, and humanistic value.
- We combine our focused experience in rare diseases with our evidence expertise to design bespoke solutions to meet regulatory commitments and drive commercial success.
- For early-stage clients, we recommend developing your strategic evidence roadmap before initiation of Phase II/III studies. This early planning can avoid downstream delays and proactively identify data gaps that may be required to secure regulatory approval or reimbursement.

We believe the ultimate success of your orphan drug requires insightful, real-world thinking early on in clinical development to address the needs of multiple regulatory and marketplace stakeholders.

About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications — from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers

For more information on Worldwide, visit www.Worldwide.com or connect with us on LinkedIn.