SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY™

Orphan Diseases | eCOA

eCOA AND ENDPOINT QUALITY SOLUTIONS FOR ORPHAN DISEASE RESEARCH

At Signant Health, we understand that orphan disease research poses unique challenges, such as small sample sizes and geographically diverse investigators. We offer unmatched scientific, clinical, and operational expertise and experience to meet the needs of your orphan disease trial. We have 20 years of experience in training investigators and ensuring quality in the outcome measures orphan disease studies are likely to require. We can support your needs for disease-specific scales, scales adapted from those used in disease-related studies, neurodevelopmental assessments, cognitive assessments, motor assessments, as well as capturing patient and family quality-of-life measures. We understand the difficulties associated with transporting sick patients to site visits and have a variety of at-home data collection methods that make patients' lives easier while ensuring collection of the highest quality data. We understand that every patient counts. We work with you and your investigators to obtain outcomes from each patient that are credible and free from undue bias and noise.

Signant Health is respected worldwide for the excellence of our offerings which include Scientific & Clinical Consulting, Rater Training & Data Quality Monitoring, an electronic scale, diary, and video capture platform, expert review services, and data quality monitoring and analytics.

ORPHAN DISEASE EXPERIENCE

Our orphan disease clinical trial experience includes global delivery of our solutions for a wide variety of indications. Some of the more recent studies have included the following indications:

- Adult Tourette Disorder
- Angelman Syndrome
- Ataxia Telangiectasia
- Cerebral Palsy with Predominantly Choreic Dyskinesia
- Dravet Syndrome
- Duchenne Muscular Dystrophy
- Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep
- Fragile X
- Myasthenia Gravis
- Neimann Pick Type C
- Pantothenic Kinase Associated Neurodegeneration
- Rett Syndrome
- Spinal Muscular Atrophy
- SCN8A Developmental and Epileptic Encephalopathy Syndrome

GLOBAL OPERATIONS TEAM

Our expert, highly experienced clinical, technical, and operational delivery teams are international. We have "boots on the ground" in 10 international offices in the United States, United Kingdom, Europe, India, and Japan. In addition, we have an extensive network of clinical disease-experts around the world.

SCIENTIFIC LEADERSHIP TEAM

Every orphan disease study team is advised by our Scientific Leadership team. Areas of expertise include evidence-based site selection, rater training and certification, electronic clinical outcome assessments, advanced predictive data analytics, and central review. By choosing us for your orphan disease study, you will receive customized support from these individuals.

Joan Busner, PhD
Clinical Vice President, Orphan Diseases and Pediatrics, Signant Health

Dr. Joan Busner has overseen the overall scientific, clinical, and strategic direction for Signant's orphan disease and pediatric solutions since 2005. For the 20 years that preceded her move to Signant Health, Dr. Busner held full time medical school faculty positions, directed two university clinical trial units, and served on active biomedical Institutional Review Boards. She is currently Affiliate Associate Professor of Psychiatry at Virginia Commonwealth University School of Medicine.

Lewis M. Fredane, MD
Clinical Vice President, Neurology, Signant Health

Dr. Lewis Fredane serves as the therapeutic area leader for neurology, overseeing Signant's eCOA, rater training, and quality assurance services. Previously, he was a practicing neurologist and clinical assistant professor of neurology at Drexel University College of Medicine in Philadelphia, Pennsylvania and has worked in pharmaceutical drug development at several companies including at Sanofi/Genzyme Pharmaceuticals, Meda Pharmaceuticals and the CRO Omnicare Clinical Research.

Anthony T. Everhart, MD
Clinical Vice President, Internal Medicine, Signant Health

Dr. Everhart is board-certified in internal medicine and a fellow of the American College of Physicians with over 23 years of experience. Prior to joining Signant, Dr. Everhart held positions as vice president, medical affairs and vice president, medical informatics at Chiltern and Covance. He has worked in all phases of clinical development in numerous therapeutic areas including allergy and immunology, cardiovascular, hematology and oncology, infectious disease and HIV, neurology, ophthalmology, psychiatry, respiratory, and rheumatology.

Alan Kott, MUDr
Practice Leader, Data Analytics, Signant Health

Dr. Alan Kott is the data analytics practice leader at Signant Health. He has worked with Dr. Joan Busner and others to develop innovative, industry leading predictive analytics programs for early detection and remediation of flawed rating techniques in pediatric and orphan disease trials.

Signant Health provides a complete electronic clinical outcome assessment (eCOA) and Endpoint Quality solution that is reliable, user-friendly, and allows you to capture data on clinician and patient rated outcome measures and event diaries, on-site or at the patient's home. Further, as many orphan diseases begin in childhood, and pediatric clinical trials are an area of extensive expertise for Signant Health, we are ideally positioned to provide tools that will capture the pediatric patient's and family's perspective with respect to efficacy, safety, and life quality. Our pediatrics team provides consultations on scales.

eCOA/ePRO

For patients, our eCOA/ePRO solution takes into account the cognitive, motor, and age-related abilities of your orphan disease population, such as large, easy to activate radio buttons.

ELECTRONIC CLINICIAN RATINGS

For site raters, our enhanced eCOA/eClinRO solution seamlessly integrates ratings guidance and automated scoring, enhancing raters' ability to provide accurate efficicacy and safety data.

ENDPOINT QUALITY SOLUTIONS

Our Endpoint Quality solutions include Scientific & Clinical Consulting, Rater Training & Data Quality Monitoring, and PureSignal Analytics. These solutions have been used for orphan disease studies to identify quality issues at the study, site, rater, and patient level in near real-time, enabling course-correction of issues that might otherwise cause the study to fail.

TYPICAL ORPHAN DISEASE STUDY CHALLENGES

The following lists the most common challenges we encounter in our work with orphan disease researchers:

- Widely geographically dispersed sites, often requiring sponsors to open sites in multiple countries
- Disease experts who have patients but often lack clinical research experience
- Investigators with idiosyncratic means of applying tools or definitions
- Investigators whose interview and assessment techniques vary widely over time and within and across patients
- Small sample sizes, making recruitment and retention especially challenging
- Lack of validated measures for the orphan disease under study
- Regulatory interest in capture of video assessments, and subsequent analysis and central review
- Heterogeneity of disease presentation
- Measuring drug-related change versus natural disease progression
- Travel burden for patients who may be too ill to visit the site
- High hopes and strong relationships with sites that may result in high placebo response

OUR SOLUTIONS FOR ORPHAN DISEASE CLINICAL RESEARCH

At Signant Health we take a comprehensive approach to address each of the above challenges.

RATER TRAINING & DATA QUALITY MONITORING

Ensuring accurate and standardized ratings is critical to the success of an orphan disease trial. Signant offers a rater training program that engages all levels of raters and investigators. It highlights the nuances and difficulties of scales for specific patient populations. For motor and cognitive assessments, a workshop approach is often used whereby raters are able to practice scale administration in small groups with guided expert feedback. We incorporate placebo response minimization and best practices for interview and assessment technique. Often raters are unaware of the role an inadvertent placebo-enhancing comment many play in patient reporting of symptoms. Role-play and discussion, as well as direct to patient videos are often used in our placebo-response minimization programs. We also conduct Clinical Global Impressions (CGI) standardization training and when indicated may recommend disease-specific annotated CGI anchor points (e.g. severity, frequency, effect on function) to increase accuracy and reliability of CGI ratings.

SCIENTIFIC & CLINICAL CONSULTING

Protocol and Scale Consultation

Our scientific leadership team is available to you for expert consultation on protocol and design feasibility, including measurements and visit schedules. Our scale management division works closely with you to obtain licenses and validated translations for international trials.

Evidence-Based Site and Rater Selection

Depending on the orphan disease under study, we may be able to assist in rater and site selection. To select sites and raters, we will consider previous performance by reviewing our Data Quality Analytics solution and historical external expert evaluations of recorded patient interviews (in which we conducted the training and monitoring). We will recommend to you experienced, skilled, and calibrated raters who have previously been trained by Signant and have demonstrated proficiency in our scale certification testing and in-study data quality monitoring.

Subject Eligibility Review

A critical step in a successful study is to assure that only eligible, appropriate subjects are admitted. We use our proprietary methodology to conduct independent review of subject eligibility, diagnostic validation, and symptom severity confirmation to determine appropriateness of each subject for the study. We will ensure that only subjects meeting the diagnostic criteria are entered into the trial. We work frequently with academic experts in orphan disease specialties to serve as independent adjudicators.

ELECTRONIC SCALE & DIARY PLATFORM

eCOA/ePRO

Signant's eCOA platform is the gold standard in data quality and reliability, and it is supported by the industry's most robust operational infrastructure. It can be used for home- or site-based ePROs, eClinROs, eObsROs, and collection of integrated wearable and sensor data. It is globally accessible via app, provisioned device, or web. It supports any combination of provisioned device and/or bring your own device (BYOD) strategy; the mobile app solution is available to use on Android or iOS devices; and it can integrate with clinical data systems, such as electronic data capture (EDC) and randomization and trial supply management (RTSM).

eCOA/eClinRO

Our proprietary enhanced eClinRO solution uniquely incorporates edit checks that warn raters of potential errors in data quality prior to data submission. Data quality is improved by additional instructions and prompts that can be built into the scales themselves. Alerts are sent when inclusion and exclusion criteria are violated after data submission, at screening, and at baseline visits. Electronic Clinician Ratings has been proven to significantly reduce errors in data (compared to paper administration) for a wide variety of indications.

Audio and Video Capture

Audio or video recordings can be captured via Electronic Clinician Ratings and assessed for eligibility, scoring consensus, and interview and ratings quality. The built-in video capture functionality allows us to monitor and, when needed, retrain site investigators to ensure the correct administration of scales. We have extensive experience in central review and central scoring and are able to capture subtle movement changes for blinded site-independent reviews as often sought by regulators for neurodegenerative and other orphan disease trials.

Signant expert reviewers undergo standardized, in-depth scale training, qualification scoring, periodic calibration, and ongoing performance monitoring by Signant clinicians. Metrics, including intra- and inter-rater reliability, can be provided at critical points in the study. We provide site videographer training to ensure capture of movement scales, cognitive assessments, and other scales requiring close and targeted camera angles.

COA DATA ANALYTICS

Our proprietary, evidence-based analytics solution can monitor and identify risks to your COA data at the study, site, and rater level while the study is ongoing. Custom algorithms identify administration and scoring errors, erratic ratings, illogical inconsistencies within eCOA data, and discrepancies across scales. Working closely with your study team, our expert clinicians interpret the findings and develop a remediation plan. We are able to intervene and deliver corrective actions, whether targeted tutorials to individual investigative staff, study-wide dissemination of additional training materials, or deeper dives into a site's performance. Proactive intervention happens when it matters, not after the study.

OTHER DIGITAL SOLUTIONS TO CONSIDER

While our endpoint quality solutions play a critical role in the development of much-needed therapies for orphan diseases, our full spectrum of digital solutions can also help study teams reach more participants, improve the patient and site experience, and optimize data quality.

eCONSENT

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ABOUT SIGNANT HEALTH

Signant Health is the evidence generation company. We are focused on leveraging software, deep therapeutic and scientific knowledge, and operational expertise to consistently capture, aggregate, and reveal quality evidence for clinical studies across traditional, virtual, and hybrid trial models. For more than 25 years, over 600 sponsors and CROs of all sizes – including all Top 20 pharma – have trusted Signant solutions for remote and site-based eCOA, EDC, eConsent, RTSM, supply chain management, and data quality analytics. Learn more at www.signanthealth.com.