SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY™

The Signal

5 Tips for Success in Rare Disease Studies

Before you begin planning your rare disease study, it's important to identify potential challenges. At Signant, we believe that the right tools and guidance can facilitate rare trial feasibility and improve data quality, thus improving the chances of trial success.

As you plan your trial, here are five tips to help you identify and successfully manage common challenges.

1. **Keep pediatric patients in mind.**

   Many rare diseases targeted for orphan drug development begin in childhood, making it essential for sponsors to design their protocols with this age group and the associated requirements in mind. Children tire easily, and longer visits, such as those at screening or baseline, may need to be split. There may need to be accommodations for travel and some families may bring siblings and other family members to visits.

   For children able to complete self-report assessments, child friendly digital platforms with the ability to accommodate "smiley face" visual analogue scales may be required. eCOA that tracks age and automatically re-provisions required age-specific scales or automatically tracks and applies age-dependent scoring algorithms as a child ages through the trial should be considered and arranged prior to initiating the trial. In addition, as proxy or parent/caregiver reports are typically central data elements, a standardized means of ensuring caregiver comprehension of scale instructions, and, for eCOA, the ability to track the consistent input of a single designated caregiver will be critical for generating credible, high quality data.

2. **Prepare for global translations and localization.**

   To be considered a rare disease, a condition must affect fewer than 200,000 people in the US at any given time, or in Europe, fewer than 5 people for every 10,000. Given the scarcity of patients, rare disease studies typically recruit from sites around the globe to achieve recruitment targets but this brings its own fair share of challenges

   For one, ensuring that scales are accurately translated is essential for scale administration consistency and the best data quality. An experienced scale management team can help your study get started faster by taking care of the more time-consuming processes, such as identifying copyright owners, locating commercially available translations, and negotiating costs or licensing for your study-specific needs.

It's recommended that sponsors obtain scale management services that follow an ISPOR-compliant process, including linguistic validation. At times regulators may ask for cognitive debriefing and you will need a scale management team able to accommodate this request. Although translations are typically only required by regulators for patient/caregiver assessments, they are strongly recommended for both clinician-rated and patient/caregiver assessments so as to reduce variability and improve signal detection.

3. **Invest in expert help for rater training and remediation throughout the study.**

One common challenge of rare disease studies is the limited pool of experienced investigators due to the very rarity of the conditions. Depending on the condition, there may only be 1 or 2 centers per country that diagnose or treat the disorder, and the experts at the center may not routinely conduct research studies.

As true for all disorders, rare or common, each clinician may have his or her own way of interacting with, assessing, and evaluating patients, and these differences, while acceptable for clinical practice, may affect ratings and reduce a trial's ability to successfully detect a drug effect. Designing a training program that acknowledges and respects clinician differences but brings cohesion for the common good of the study is a challenge that will require thought, experience, and expertise.

Once trained, it's important to prevent "rater drift" or the tendency to diverge from the initially agreed upon training. To reinforce trained conventions throughout the life of the trial, sponsors should consider pre-specified refresher training and consensus opportunities, and may also wish to choose an eCOA solution with built-in pointers and guidance to guide raters as scales are administered. Many of today's eCOA solutions contain reminders as well as automated scoring to further improve data quality. Some are also able to videorecord assessments for subsequent independent review, scoring, and/or rater remediation by experts.

4. **Prevent excessive placebo response and expectation bias.**

Excessive placebo response is a major concern in rare disease studies. Many rare diseases have few treatment options and often devastating illness effects. The level of hope among patients and families is understandably high, and this is further heightened when the patient is a child. If not managed well, such expectations can lead to placebo response rates that prevent the study from demonstrating the effects of the investigative treatment. It is critical to teach investigative sites effective strategies that allow them to work with patients and their families in a compassionate manner while preventing placebo response.

In addition to investigative site training, there are placebo response mitigation training programs targeted to patients and their families. Such programs are designed to help patients and caregivers understand their role in the study and the value of objective reporting.

5. **Leverage remote technologies.**

There are a variety of reasons for conducting rare disease visits virtually. Patients may be too ill to travel or wide-spread sites may require long and burdensome travel. Recently, the pandemic-associated lockdowns may also make travel impossible or ill advised.

When designing their study protocol, sponsors should consider remote assessments and the technology necessary. Telemedicine solutions are great tools to connect patients and experts more easily. When functional unblinding (tell-tale side effects) threatens the integrity of a trial, you may wish to use a remote group of experts ("central raters") rather than site raters to conduct key assessments. Today's remote technologies allow for remote assessments, video capture, and central ratings through a variety of secure digital platforms.

For more information on rater training and digital solutions to help your upcoming study succeed explore Signant's orphan disease brochure.

You can also meet our experts, who can help you customize a range of solutions, such as identifying and proactively addressing trends within incoming scale data using a a risk-based, blinded monitoring approach.

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