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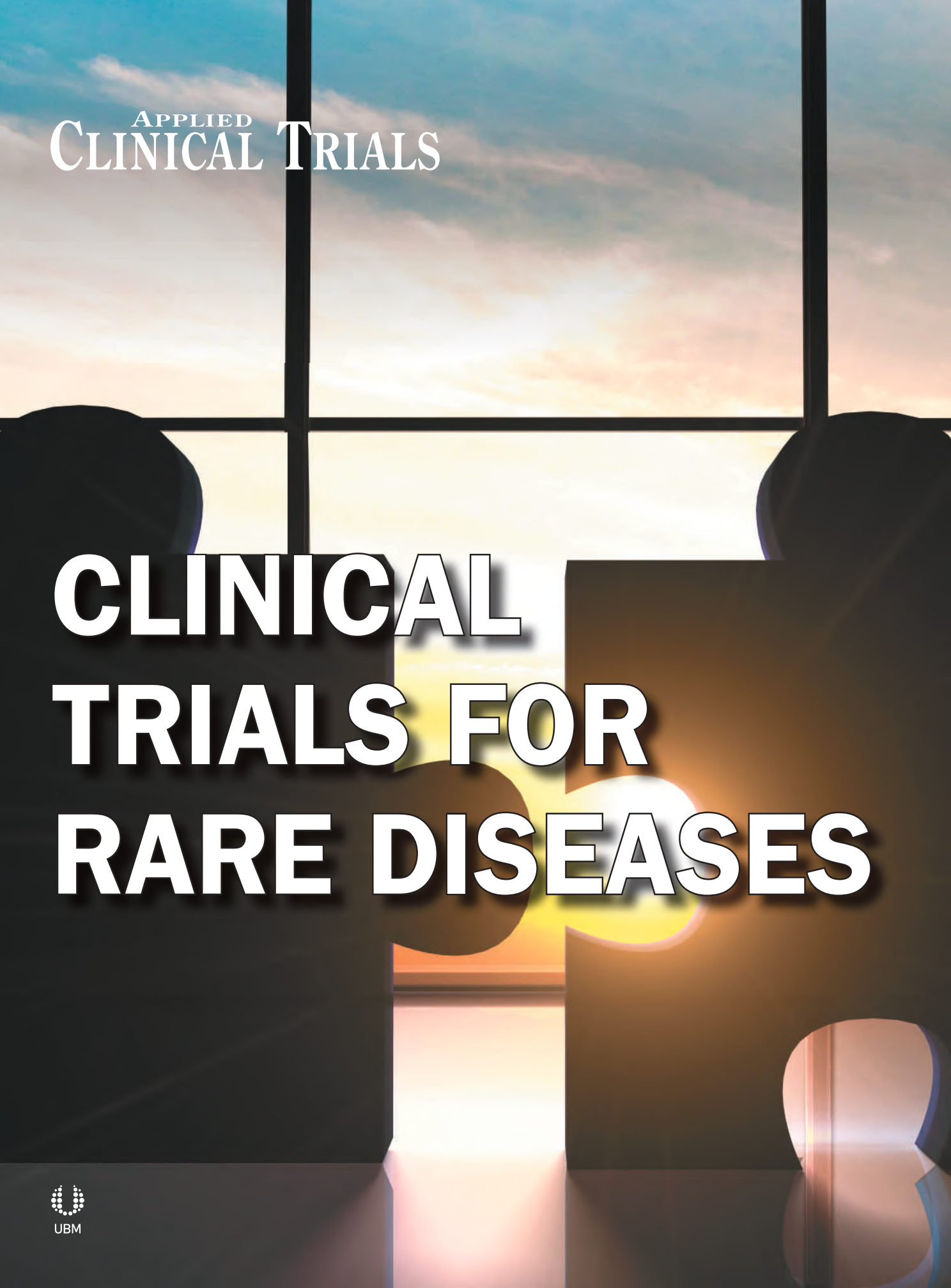

# CLINICAL TRIALS FOR RARE DISEASES

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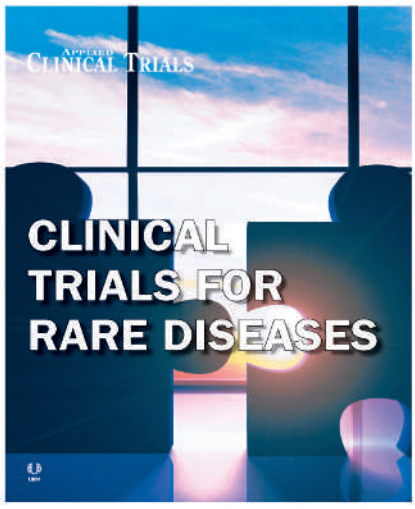


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## TOC



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*Applied Clinical Trials* is the authoritative, peer-reviewed resource and thought leader for the global community that designs, initiates, manages, conducts, and monitors clinical trials. Industry professionals learn effective and efficient solutions to strategic and tactical challenges within the tightly regulated, highly competitive pharmaceutical environment.

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# The Patients to Find the Cure

Bonnie A. Brescia

## Advancing rare disease research is a group effort and can benefit the entire drug development ecosystem

*"As his parents and his caregivers, we had to make the best decisions under the worst of circumstances, knowing that in the end we might only extend his life by a little, or improve what time he had left."* – Roberta Carlson

These are the sobering words of the mother of a teenaged son who died after a wrenching, 27-month battle with a very rare and aggressive brain cancer. Hers is just one voice among the hundreds of thousands of Americans caring for a child who is fighting one of the nearly 7,000 recognized rare diseases for which there are no known treatments. With no available treatments, turning to a clinical trial was their only option.

Like the vast majority of these parent caregivers, Roberta Carson of Chestnut Hill, Massachusetts, connected with other families facing the same devastating reality. The details vary, yet the diagnoses feel comparably grim. The decisions that need to be made accumulate, and the ability to keep tabs on every detail diminishes with each visit to the doctor or hospital—even within the closely monitored setting of a clinical study.

When working on rare disease research studies, every potential participant is so important to the study's success that sponsors and investigators are willing to go to extremes to improve access to the study. But it cannot stop there. Clinical trial teams need to address the question: How do we plan for exceptional service to the patient and their caregivers across the continuum of study awareness, enrollment, participation, and study follow-up?

### Appreciating every patient's experience

"The day-to-day experience extends beyond what may be the focus of a particular treatment, so it's critically important to have an understanding of the disease from the patients' perspective when developing the clinical and study design," counsels Pamela Gavin, chief operating officer of the National Organization for Rare Diseases (NORD). "Sponsors must recognize that not all rare disease patients are the same. Some patients are strong advocates and others are not. Some are comfortable expressing a strong voice, while many others need to address the day-to-day challenges and focus on other aspects of their lives," she added.

In the U.S. alone, rare disease advocacy groups number more than 8,000—the vast majority of which have been founded and staffed by individuals and family members faced with a rare, often little-understood disease. "A rare disease diagnosis can immediately thrust you into another world; a world where you have to become an expert in biology, genetics, scientific and clinical research, drug development, regulatory affairs, and advocacy," Gavin says.

Dr. Paul Goldberg, senior vice president of clinical development at Xenon Pharmaceuticals—a British Columbia-based biopharmaceutical company studying rare diseases with extreme traits—believes that committing to patients is a necessity as we work to understand the genetic architecture of rare diseases. "In working with families and patients with rare diseases," he says "it's really all about relationship-building. All too often, patients

and their families are alone and isolated, and often ostracized, much of which stems from incredible lack of awareness around their disorders."

Supporting patients with rare diseases requires a level of intimacy and empathy with the patients and most often their extended families. Most biopharmaceutical clinical study teams are supported by a few members with extensive knowledge of the disease, its treatments, as well as past and current research. Advocacy groups, physicians, patients, and study participants agree in their call for all members of a research team to spend time—hours, if not a day or two—with a family living with the condition under study. "Intimate knowledge is very empowering to study teams," Goldberg maintains. "I firmly believe that rare disease patients should play an important role in study design. I'll go as far to say that you can't really do [rare disease clinical research] if you don't have them participating in study design."

According to Sarah Mandracchia, director of media and research at patient and site engagement firm BBK Worldwide, this deep understanding is best practice for all clinical research programs. "Yet, for rare diseases where a patient's medical needs are not being met or treatments are unavailable, the requirement for this deep understanding is intensified and requires careful, purposeful implementation."

By taking a more active role in supporting rare disease communities, Gavin believes that sponsors can more fully understand the strengths and limitations of the patients, family members, and organizations that are supporting their research efforts.

"Text books are very good at getting an accurate picture of the classical presentation," Goldberg adds, "but they can't tell you what's meaningful to the patient."

## Driven to participate

Perhaps nowhere more so than in rare disease research are patients interested in participating in clinical trials—yet the obstacles of awareness and access remain challenging. This is not news. "As early as 2001 when BBK Worldwide conducted the "Will & Why" survey, lack of information about the opportunity to participate in clinical trials was the leading barrier to participation," Mandracchia reports. "Ninety percent of Americans surveyed said they would be open to participate in studies. And when the "Will & Why" study was conducted in the EU in 2004, willingness to participate averaged over 70%," she continues. Since then, organizations including the Center for Information and Study on Clinical Research Participation (CISCRP), Tufts Center for the Study of Drug Development, the National Institutes of Health (NIH), and numerous others have explored this problem.

The January 2016 issue of *Trials* features results of a survey of patient attitudes toward participation in clinical trials conducted by researchers at the Gastrointestinal and Lymphoma Unit at the Royal Marsden in the U.K. Of those surveyed, 88% agreed to participate in a clinical trial. According to the research report, multiple factors influenced patients' decisions to participate in a clinical trial. When patients were asked to indicate their main reason for trial participation, a belief that "the trial offered the best treatment available" or that "the trial results could benefit others," were the most frequent responses.[1]

Across the board, these studies show that willingness is not the barrier to enrollment. Awareness, opportunity and access are keys to successful study enrollment—a shared goal for researchers and rare disease patients alike.

Goldberg's concerns about lack of awareness around rare diseases runs deeper than just research opportunities. "There are multiple unique and substantial challenges, all of which we need to recognize and work to address. Chief among them is the lack of awareness," he confirms. "There is a dire need for improved education around rare disease, particularly in the medical community." For many rare diseases, there are few, if any, medical experts more knowledgeable than the patients themselves. There is little "big data" for most rare diseases.

In many cases, people knowingly are entering trials with little hope of saving themselves, but have a strong desire to move science forward.

Dr. Chris Landon, CEO of the Landon Pediatric Foundation, cares for patients with advanced diseases who, he says, "will miss the beneficial effects of early intervention. The commitment by organizations such as the Cystic Fibrosis Foundation that no patient will be left behind, drives continued development of treatment and rescue therapies."

"Another way in which patients and families can uniquely contribute to rare disease research is by participating in well-designed natural history studies intended to document the natural progression of disease and inform therapeutic development. Sponsors can make a large impact by supporting such studies," Gavin says.

## From willingness to study enrollment

Within the community of rare disease patients, access to studies is a higher hurdle than willingness to participate. Sometimes study access is a matter of logistics: patient and family fatigue is an area in which rare disease sponsors can easily be more patient-centric. "From protocol design to retention programs, rare disease trials need to consider options that might not be necessary for another study, such as concierge services for patients traveling to and from study visits or patient ambassadors to assist patients through their trial journey," Mandracchia says.

For other patients, lack of access translates into fear of not "qualifying" for a study, which can lead to some unintended consequences for the clinical trial. "Difficulties in clinical trials wind around a delicate thread—there are patients who underperform on baseline tests to 'get into' a trial or others who arrive tired after traveling a distance and perform better when

they return for follow-up. Unfortunately, if these participants have been on the placebo medication or standard of care and this 'false improvement' occurs in a better rested child who can perform a pulmonary function test with full force, the results become insignificant and the trial and drug development may come to a halt," Landon cautions from experience. "The difficulties arise in a rare disease of identifying the primary endpoint in a trial in which the downhill course of the disease makes for a very narrow window of intervention," which may further limit opportunities for trial participation.

And for families such as the Carsons, lack of access can mean absence of any relevant research. Where once study sponsors would talk about finding the "needle in the haystack" that was a qualified patient, in the case of rare disease patients, the relevant study is their needle to be found. Yet, there are so many studies underway that it can be difficult and overwhelming for patients to learn about appropriate study options. "The websites and matching services that are available today aren't designed for non-medical professionals, making it hard for the average patient to navigate and understand," Carson says. "When our son Zach was taken out of his first trial, he was considered too sick for most other trials." The family had a care team that was committed to connecting its patients with clinical trials—even those for which they were not serving as investigators. "It took our oncologist a month to get him enrolled in another trial—an agonizing month of worry."

## Delicate balance: Care, cure, and cost

Although much has been written about the high cost of therapies for patients with rare diseases, the societal debate is just beginning. Each time one of these treatments achieves regulatory approval, as Novartis' cancer drug Kymriah did in August, we are confronted with a dilemma. We have the science to curb or cure more and more rare diseases, and we enthusiastically welcome these achievements, as *The New York Times* did, describing Kymriah as "spectacularly effective against a rare form of leukemia, bringing remissions when all conventional options have failed." But the treatment will cost $475,000. And a child may live a long, productive life.

As a practicing pediatric pulmonologist, Landon has seen the survival for an infant with cystic fibrosis increase from two years of age, to 12, to 19, up to the current normal life span for some genotypes with available pharmaceutical intervention. Yet, Landon recognizes the pull between patients, families, and caregivers who need to see a change in the arc of their disease and insurers or government payers who have set much different targets.

Goldberg and the Xenon team are working to dissect the determinants of inherited, familial forms of rare disease. The opportunity to get to the root cause of these rare conditions often leads to better understanding of the pathophysiology itself, in turn leading to more directed and specific therapies. "By defining novel pathways for one disease, we often reveal critical determinants of other diseases," Goldberg says.

By studying rare diseases, we learn about the most basic causes of disease. "Rare diseases become important teachers about common ones; they help us to identify critical biologic pathways, and systems that are otherwise difficult or impossible to discern," NORD's Gavin says. "It can accelerate discovery and development, and a drug that may be developed for rare disease may be as or more effective for its more common disease cousins. The development of therapeutics in rare disease benefits us all—not just the one in 10 of us living with rare diseases."

*"Devastated to lose our son Zach, we did take some comfort knowing that we were contributing to research that might someday lead to a treatment or a cure."* – *Roberta Carlson*

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**Bonnie Brescia is a founding principal of BBK Worldwide and is widely recognized for helping to shape the patient recruitment and engagement discipline. She can be reached at bbrescia@bbkworldwide.com**

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# How to Overcome Barriers in Rare Disease Drug Development

## Facing challenges and evolving approaches to advance needed therapies

Tremendous opportunities await clinical drug developers in advancing therapies for thousands of rare diseases. There are more than 7,000 different rare indications across multiple therapeutic areas affecting the lives of millions of people, and treatment options are only available for a few hundred of these indications. Trials in rare indications are particularly challenging because they involve small groups of diverse patient populations, most disease indications are poorly understood, and standard of care is routinely not available. Researchers often face numerous challenges in their efforts to advance much needed therapies.

Traditionally, trials in rare diseases have not been as attractive to researchers as trials in more common diseases that affect larger patient populations. Most rare indications are complex and tend to enroll slower and have higher drop-out rates, which contribute to longer development timelines and higher drug development costs. However, the focus is shifting as drug developers identify favorable regulatory pathways to approval.

PRA Health Sciences has been at the forefront of drug development in rare diseases. Through its experience working in multiple rare diseases and contributions to the market approval of 16 drugs to treat patients with rare indications, it understands the unique barriers to trials involving small patient populations. Overcoming these barriers requires a special approach; one that listens to and understands the needs and perspectives of all stakeholders—patients, their caregivers, advocacy groups, and investigators—and incorporates their voices into the global clinical trial planning process.

Scott Schliebner, Vice President, Rare Diseases – Scientific Affairs at PRA Health Sciences shares his insights to help guide the future development of rare disease clinical trials.

**1. Poor enrollment and retention rates increase the cost of drug development and have had a profound effect on the attractiveness of clinical drug development in the rare disease space. What do you see as the major issues when it comes to enrolling and retaining rare disease patients?**

We know that finding eligible patients for trials involving small patient populations and then retaining them throughout a study is a major concern for most drug developers. Rare disease trials tend to accrue fewer patients over a wider geographical area causing patients and families to travel longer distances to sites. These patients often have debilitating conditions, and many of them are children who need assistance from their caregivers to get them to site visits. Caregivers may have to take time off work and incur costs for travel, lodging, and other expenditures, which may prohibit the patient's ability to participate. Once enrolled in a study, meeting study requirements may become extremely difficult for some families and make participation impossible causing the patient to drop out.

**2. Patient retention in clinical trials is always a top concern for researchers. Why do you think patient drop-out rates tend to be more problematic in rare disease trials, and what do you suggest we do to improve retention rates?**

It's not always easy for patients and their caregivers to adhere to strict study protocol requirements that don't take into account their specific needs. Historically, researchers have assessed patients' needs after the study protocol is finalized, and investigative site staff develop recruitment plans based on their perspectives alone.

We are learning that rare disease trials require a different approach; one that considers the special needs of patients and families and makes trial participation as easy as possible. To ensure compliance and limit drop-out, drug developers must listen to their experiences, include them in the initial stages of protocol and study design, and ultimately make the study requirements less disruptive to

**Scott Schliebner**
Vice President
Scientific Affairs - Rare Diseases
PRA Health Sciences


the patients and their caregivers. It is extremely challenging to incorporate this input after the study protocol is finalized or once a study is underway.

**3. Accelerating clinical drug development in rare diseases and getting needed therapies to market faster is a significant challenge for researchers. Knowing where a new trial fits into the current disease landscape can mean the difference between success and failure. What do drug developers need to know to effectively position a new trial in this already highly competitive clinical trial environment?**

Determining how a program fits into the rare disease space is not easy and requires thorough planning. For drug developers to understand where their trial best fits, they must first understand where open studies are located, which ones are real competitors, and which ones could serve as feeder studies for a new trial. Leveraging public, private, and proprietary data sources to drive trial design, identifying the investigators who treat the most patients, and understanding treatment trends are significant. These strategies can help drug developers position their trial effectively.

**4. There are many barriers to overcome when placing a new trial in the rare disease space. What can drug developers do to minimize these barriers and drive rare disease programs to better patient outcomes?**

Our approach to rare disease drug development is evolving, and we have begun to recognize the value of input from a variety of stakeholders. These stakeholders understand the barriers patients face and can provide us with insights into minimizing them. Each stakeholder offers a different perspective. Listening to their voices and engaging them early in the study design planning, positioning trials, and engaging patients can help us to minimize potential barriers and drive clinical programs to better outcomes.

Learn More

# The Virtual Opportunity in Rare Disease Trials

Karen Kaucic, MD, Horacio Plotkin, MD, Christopher Komelasky

## Challenges in rare disease research can be solved with virtual trials and their supporting technologies

Special challenges in rare disease research—small, geographically dispersed patient populations, the predominance of pediatric patients and the great economic demands of traditional site-based trials—make virtual trials ideal for rare disease drug development. Virtual trials reduce or even eliminate travel to study sites, making it possible to conduct rare disease studies that cannot otherwise be undertaken due to logistical and economic barriers.

Digital health technologies, including Internet-based communications, smart devices, and mobile health (mHealth) technologies, are transforming trial operations to enable remote patient enrollment and data collection—solutions that offer unprecedented opportunities to advance both rare disease research and virtual trial models. Early applications of remote technologies, together with a positive regulatory climate, promise rapid adoption in rare disease research—an advance that could make dramatic progress to address more than 7,000 identified diseases, 90% of which currently lack specific treatments.[1]

### Brick and mortar vs. virtual operations

In traditional site-based trials, time to site activation averages one year at costs ranging from $20,000 to 30,000;[2] during a trial, site maintenance averages $1,500 per month.[3] Patient recruitment—typically a major bottleneck—accounts for the lion's share of study delays. An estimated 11% of sites fail to enroll a single patient;[2] less than 10% of trials are completed on time.[4] Efficient time and cost management depends upon enrolling the largest number of patients at the fewest number of sites. In the rare disease setting, site-based subject enrollment and data collection pose the opposite efficiency scenario—fewer patients enrolled by more sites. By definition, rare diseases affect fewer than 200,000 people in the U.S.;[5] the EU considers a disease rare if it affects five or less in 10,000.[6] In one example, a trial of a treatment for ANCA vasculitis expects to involve 200 centers in order to enroll the 300 patients required.[7] In a 2014 survey of 2,759 rare disease trials registered on ClinicalTrials.gov, actual enrollment in the majority of trials (955) was fewer than 50 patients.[1]

In concept, the virtual trial brings research to the patient—a perspective of great value in rare disease research.[8] Remote data collection would eliminate geographic barriers and reduce the costs of traditional site management. In a rare disease study, a virtual trial could include:

- One clinical site and virtual study coordinating center to manage medical issues and all study operations, including clinical trial materials management and multiple stakeholder engagement: trial management supported by a real-time data management platform for monitoring, tracking, reporting, and analytics.
- Online patient recruitment, screening, and enrollment via disease-specific online registries or social media sites: health data access via physician and electronic medical records (EMRs).
- Electronic informed consent supported by telemedicine meetings with patients and families.

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•Remote, at-home data collection via electronic patient reported outcomes (ePRO), research-grade sensors, and smartphones to take measurements and transmit data directly to investigators.
•Virtual patient visits: initial and interim visits conducted via telemedicine for training, to oversee use of sensors and devices, adverse event reporting from patients to sites, and manage protocol compliance. In fact, replacing some in-person visits with virtual visits may be a next transitional step for much of the industry as it heads toward the complete virtual trial.
•Remote patient prompts and information via smartphones and other devices to support engagement and retention and facilitate follow-up activities.

Patient access is the greatest advantage of virtual models in rare disease research. Widely dispersed patients can participate in trials regardless of their location and their physical ability to travel. In addition to the obvious benefit of reduced site costs, virtual trials collect real-world data during the patient's everyday activities. This increases the likelihood that study findings will more closely reflect therapeutic effects in real-world use. With traditional dropout rates as high as 30%,[9] virtual studies can improve retention by offering greater convenience and continuous patient-centric communications and support.

## Coming of age

Virtual trial initiatives began with Pfizer's 2011 pilot study, "REMOTE." Conducted under an investigational new drug application, the randomized REMOTE trial used online informed consent and remote data collection to evaluate an overactive bladder therapy. The goal was to determine whether the virtual model could replicate findings of a previously conducted Phase IV site-based trial. As a first attempt to change years of traditional clinical trial conduct, REMOTE failed, due to insufficient enrollment, but demonstrated that electronic informed consent, distribution of blinded investigational drug to patients, and remote data capture is feasible, both from operations and regulatory points of view.[10]

Following REMOTE, a host of studies piloted trial operations using virtual technologies, building necessary experience to validate the feasibility, accuracy, and security of remotely conducted trials. In 2015, the virtual trial came of age with "VERKKO," conducted by eClinical Health and Sanofi.

The European-based VERKKO trial enrolled 60 patients recruited on Facebook to study the use of a patient-centric, online clinical trial platform that integrated a 3G-enabled wireless glucose meter. Study materials were mailed to patients, who took measurements using the smart glucose meter. The smart device transmitted data to the trial platform, which made findings available for real-time review by the coordinating site and patients. VERKKO was managed at a single site by one investigator and one study nurse.

Results of the successful trial reported in 2016 provided evidence for the presumed advantages of remote designs. In post-study surveys, patient satisfaction earned a positive score of 4.5 out of 5. Compared to a site-based comparator study, the virtual trial improved protocol compliance by 18%; increased patients' glucose profiling time by 22%; and reduced study site's time for study coordination activities by 66%.[11]

## Virtual technologies

Virtual research capabilities have matured with the increasing availability of and patient familiarity with a broad array of digital health technologies—telemedicine, intelligent devices, and mobile health technologies, including smartphone-based software applications (apps) and wearable sensors.[12] Forty-three percent of these health-related apps are designed for healthcare professionals to conduct remote health monitoring and disease management.[13] And the number of telemedicine visits continues to climb. For example, Teladoc, just one of the many providers of telehealth services, recorded almost one million visits in 2016, which is 65% more than a year earlier.[14]

The integration of health monitoring devices with smartphones has generated medical-grade mobile technologies to measure heart rate, blood pressure, respiration, ECG, core temperature, and galvanic skin response. "Intelligent" devices transmit data directly to the caregiver or research site. Among the most widely used are a mobile telemedicine system that interfaces with a computer server to record and report video consultations; a fetal heart rate monitor used with a smartphone for data transmission, and a smartphone image transmission system used for diagnosis.[15]

## Virtual solutions

Rare disease patients are well attuned to Internet-based support communities and rely heavily on social media for disease-specific information and research opportunities. Rare disease research has been a major catalyst in patient-centric trial design. In-home clinical trial support programs, which field good clinical practices (GCP)-trained nurses to collect trial measurements during home visits, are already a feature of rare disease studies. The rare disease community is well positioned to be a rapid adopter of virtual trials.

**Recruitment.** RareConnect, Inspire, PatientsLikeMe, RareMark, and OneVoice are just a few of the online communities now being leveraged to identify and recruit rare disease patients. Disease-specific social media sites, registries, advocacy and support groups, and research consortia have demonstrated power to identify and maximize enrollment of scarce, geographically dispersed patients. Enrollment speed is another important benefit. In a single week, the rare disease social networking site Inspire identified 18 potential subjects for a Mayo Clinic rare disease study that hoped to enroll 12 participants.[16]

**Reduce patient and caregiver burden**. Remotely conducted trial operations eliminate the stress, time loss, and costs of traveling to a site for multiple visits. This is especially important for rare disease patients. Children comprise roughly half of the rare disease population, and care depends on complex treatment and support networks. In addition to family members, stakeholders often include primary care physicians, multiple medical specialists, physical therapists, and home care providers. Difficulties posed by travel, disruption of care routines, and lost days of school and work are major barriers to trial participation.

**Protocol compliance and retention.** Virtual models provide ongoing support and information for compliance-related matters and engage patients throughout the trial. Online communications, smartphones and mobile health technologies deliver prompts that direct patients to adhere to protocol. Smart devices signal times to take measurements, and telemedicine visits are used to observe health status, elicit questions and provide support to engage patients. The convenience of in-home research is a compelling advantage, encouraging both participation and retention.

## Next steps: progress and challenges

Rare disease studies are among the first generation of virtual designs, some of which include several onsite clinic visits in addition to virtual visits. The Lunasin Virtual Trial, launched recently by online patient community PatientsLikeMe and the Duke ALS Clinic, enrolled 50 ALS patients in only five months. Participants will make three clinic visits and monthly virtual visits via PatientsLikeMe to collect measurements for weight, evaluate the Lunasin regimen, and complete a PatientsLikeMe-developed PRO rating scale during the 12-month trial.[17] Science 37, a developer of site-less trial models, used its "metasite" virtual platform to speed enrollment of a Phase III trial for the rare disease pemphigus vulgaris—an autoimmune disorder of the skin. The virtual site enrolled 30% of the trial's subjects 20 times faster than the rate expected for the 60 traditional sites conducting the study.[18] More recently, Transparency Life Sciences partnered with researchers at Mount Sinai to test the feasibility of replacing in-person study visits with virtual visits using a telemedicine platform. The research concluded that telemedicine-enabled studies are feasible and can overcome the enrollment challenges of geographically dispersed populations.[19]

Regulation is advancing as mHealth technologies offer benefits of patient access and lower research costs, although it will take time and experience to address all the issues posed by the emerging digital health environment. Issues range from cyber security to the acceptability of a given mHealth device for use in a clinical trial setting. In the U.S., the FDA's 2015 Mobile Medical Applications guidance is being further assessed in light of the 21st Century Cures Act of 2016, which clarified regulation of medical software and amended the definition of "device." The FDA is in the process of gathering information on the use of mobile technologies in research and is developing draft guidance on oversight for medical device software.[12]

Sponsors will be challenged to manage changing—and varying—global regulation as rare disease studies adopt virtual designs to access patients worldwide. Virtual study coordination centers will be aided by increasingly sophisticated IT platforms with capabilities to integrate telemedicine, smart devices, and mHealth data and to efficiently manage remote recruitment, screening, consent, and patient prompts across global sites. Experience using such real-time, integrated platforms is still relatively limited but will increase as virtual practice expands.

Buoyed by expanding scientific knowledge, accelerated regulatory pathways, and monetary incentives, rare disease research delivered 30 new therapies and accounted for more than 40% of new drug approvals in 2015 and 2016.[20,21] With an estimated 560 agents in the development pipeline, virtual trial models hold the promise to significantly expand delivery of novel therapies to waiting rare disease patients.[22] Virtual trials will advance the operational efficiencies and, more importantly, increase the feasibility of drug development for rare diseases.

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# Using IRT to Address Rare Disease Supply Chain Challenges

Amy Ripston

## Rising complexities of randomization and trial supply management in small, specialized patient populations

Due to the smaller patient populations, rare disease patients can be scattered globally for any given trial. This complexity alone is a burden to patients that may not have local treatment options and introduces supply chain logistical challenges to the manufacturers.

Rare disease trials typically involve biologics, or large molecule drugs, or increasingly peptides. These newer drugs often don't have the manufacturing schedule or predictable shelf life that many of the smaller molecule drugs have. Many of these drugs require special handling, temperature control, and quick turn-around due to short shelf lives. Because of the nature of the drug, and sometimes the severity of the disease, treatment may need to begin within 24 hours of enrollment. Enrollment itself may be unpredictable, so the supply chain must be robust enough to support patients when and where they enroll, globally. Given that small patient populations also equate to smaller dose quantities, the importance of an air-tight supply chain is heightened.

To address these challenges, it is crucial for manufacturers to have a robust IRT or randomization and trial supply management (RTSM) system in place.

### What are the essential IRT capabilities to support rare disease trials?

1) *Complex site initiation and randomization capabilities.* Given that rare disease patients may travel significant distances to participate in a study, the randomization and trial supply management system needs to be ready at all times; because, asking the patient to return isn't a reasonable option given the effort that they put forth in getting to this point in the study. Adding to the complexity is the drug delivery devices themselves, as some rare products require up to 40 preparation steps prior to administration to the patient.

To ensure randomization can happen at short notice, in some cases, manufacturers may pre-initiate sites to enable them to finish essential documents and enroll the patient within a 24-hour period. The IRT supports this by being able to stage drugs at a significant number of depots around the world so the drug could be overnighted to sites when activated. The IRT systems also need to be able to manage the supplies at both the sites and the depots effectively.

2) *Flexibility built into the system.* Many traditional IRTs are rigid and require added time and resources to allow for adjustments during the study. A modern, flexible IRT is needed to quickly adapt to changes in patient population, enrollment, site location, etc. For example, as patients are dis-

> **Another complexity that requires flexibility is the adding or dropping of countries within the study. Switching countries may mean varying supply regulations and even supported languages.**

persed around the globe, many will need to travel significantly to get to the study sites. If by chance a new site opens that is more convenient for the patient, the IRT must be able to easily transfer the patient and all their resulting supply needs. Another complexity that requires flexibility is the adding or dropping of countries within the study. Switching countries may mean varying supply regulations and even supported languages.

3) *Resupply capabilities and supply chain scenario planning*. IRT systems are crucial to the overall management of supplies from receipt of the depot to destruction per the manufacturer's instruction. It is becoming an increasingly valuable component of a study's supply chain.

Biologics present many supply logistics challenges from production to distribution and storage.

> **Many of the new supplies don't have established shelf life dates and are submitted to sites on a stability protocol.**

While all supply chain management in the clinical realm has its challenges, biologics manufacturing has even more complexities, including a higher incidence of production issues. The drugs that do make it to the sites have a short shelf life, sometimes only a few months. This puts an additional burden on the IRT system to ensure that patients are not using any product beyond their intended shelf life date. To make supply management even more challenging, many of the new supplies don't have established shelf life dates and are submitted to sites on a stability protocol. At any specific pull-point, the product may be in or trending out of specifications. If it is trending out of specifications, the IRT system needs to quickly adapt to ensure that study drug is returned per the manufacturer's instructions.

> **A robust IRT should have advanced supply forecasting and scenario planning functionality.**

Another supply consideration is linked to enrollment projections. If enrollment outperforms predictions by even an additional 500+ patients, with a rare disease trial, this could double capacity. The complexity of the product may not allow for the speed of turnaround that would be needed. A robust IRT should have advanced supply forecasting and scenario planning functionality.

4) *Temperature control management*. Biologics need to be temperature controlled during transit and storage. Therefore, a robust IRT is needed that reacts quickly to any shipment that has been identified by the site, and confirmed by the sponsor, as being outside of the product's storage condition.

5) *Online drug accountability, returns, and destruction*. A robust IRT system is needed to track these drugs through a very complex and evolving supply chain. Sponsors are using drug dispensing records from the IRT, from receipt to destruction, to strengthen compliance capabilities in the event the site is audited.

Additionally, tracking the drug may not stop after the close of the clinical trials and the approval of the drug. Once the drug is approved, you may end up with a post-commitment trial. A robust IRT should be able to handle the switch from investigational to marketed drug.

The IRT is a critical component to ensuring you have an air-tight supply chain for your rare disease trial. The system needs to handle complex randomization, have the flexibility to adjust with the evolving trial scope, and offer significant capabilities in resupply and supply scenario planning.

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# Optimizing Rare Disease Outcomes through eCOA

Susan M. Dallabrida, PhD

## With technology and training, eCOA can improve rare disease data trial collection

Clinical outcome assessments (COAs) are considered by the FDA to include "any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit."[1] While treatment efficacy can be measured in many ways, COAs in clinical trials must represent meaningful outcomes for patients regarding the effect of their condition and how the treatment makes them feel, function, or survive.

However, selecting and validating COAs for rare diseases can be particularly challenging, often because there are no new or condition-specific validated outcomes instruments (Table I). And, because disease presentation, course, and response to treatment within each disease vary greatly, it can be difficult to recruit a sufficient sample within the small patient populations for initial COA instrument development and validation studies as well as for later data collection.

Sponsors also need to consider that the common age group (especially for children) and presence of physical and/or cognitive disability within rare disease patient populations may warrant innovative modes of administration and alternative forms of COA such as Observer-Reported Outcomes (ObsRO) and/or Performance Outcomes (PerfO).

> It can be difficult to recruit a sufficient sample within the small patient populations for initial COA instrument development and validation studies as well as for later data collection.

> Missing data and nonstandard data collection are the largest threats to data quality.

### Improving COA Data Quality in Rare Disease Trials

Quality data are essential to ensuring effective and appropriate measurement of treatment outcomes. This becomes even more important in rare disease trials, where the limited availability of eligible clinical trial patients could affect a study's statistical power. Every patient matters, and the quality of the data that they provide is of the utmost importance.

However, collecting high-quality data in rare disease clinical trials can be difficult for many reasons. Missing data and nonstandard data collection are the largest threats to data quality. Additionally, inter-rater variability and variability in the rater's understanding of the assessment contribute to poor-quality data. This is particularly true because any rater bias, including the halo effect, stereotyping, perception differences, leniency/stringency, and scale shrinking is exacerbated—and can be particularly damaging to the quality of rare disease data collected.

**Table 1.** Roadmap to developing clinical outcome assessments (COAs)[6]

| 1. UNDERSTANDING THE DISEASE OR CONDITION | 2. CONCEPTUALIZING TREATMENT BENEFIT | 3. SELECTING/DEVELOPING OUTCOME MEASURE |
|---|---|---|
| **What is known about the condition?**<br>• Natural history data may be limited<br>• Heterogeneity in clinical manifestations over time and by disease subtype | **What constitutes meaningful treatment benefit?**<br>• ID of a single concept of interest (COI) may be difficult due to heterogeneity of RD sub-populations<br>• A responder to treatment may be defined differently across subgroups<br>• Direct measures of treatment benefit (how patients feel and function) may not be possible | **Are there any extant COAs that are appropriate?**<br>• The answer is usually "no"<br>• Modification of extant COAs is still time-consuming, but usually quicker than development of a new COA<br>• Time and resources may not be available for modification or development of a new COA |
| **How is it treated?**<br>• Disease-specific treatments may not exist<br>• Treatment variation across regions, age, groups, payers, subgroups | **How will the clinical study be designed, i.e., the context of use (COU)?**<br>• Difficulty with patient recruitment results in less restrictive entry criteria to achieve maximum sample size possible<br>• Need for creative study design and analysis | **How to develop or adapt the COA for context of use?**<br>• Traditional methods may not be feasible<br>• No one size fits all solution exists<br>• Difficulty with recruitment for patient engagement and qualitative research<br>• Need for creativity in COA development methods |
| **How does condition impact patients and caregivers?**<br>• May differ by disease stage, subtype, age, region<br>• Little data may exist | **Which COA types are needed?**<br>• PRO measure often unfeasible<br>• ClinRO measure may need to be general in nature<br>• ObsRO measure must be based on observations—not proxy measures<br>• PerfO measure development standards are not established | **How to establish measurement properties for context of use?**<br>• Traditional psychometric methods are not designed for small sample sizes<br>• Stand-alone validation studies are likely unfeasible |

Because of its proven ability to reduce missing data, increase event reporting, and improve accuracy in reporting, electronic clinical outcome assessment (eCOA) is the most effective method for capturing validated, consistent assessments to measure rare disease trial outcomes.

eCOA systems are preferred over traditional paper-based methods by clinical trial patients[2] and utilize alarms as reminders for patients to complete assessments; this consistently drives more complete data collection than paper COA (Figure 1)[3]. In addition, eCOA systems are typically built with system checks that reduce missing data, delivering more valid data for the trial sponsor's evaluation.

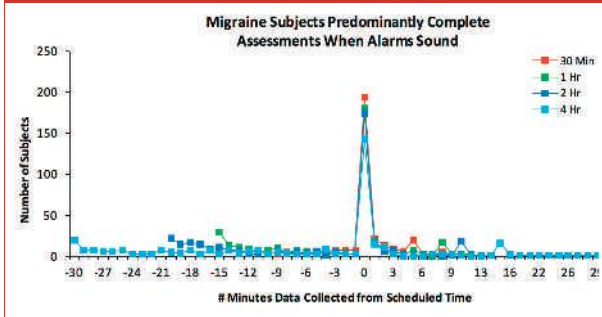
Overall, these features improve data quality, and ultimately, the statistical power of rare disease studies. As a result, fewer patients are required to determine a treatment's efficacy and safety, enabling trial sponsors to reach go/no-go decisions faster.

Additionally, most eCOA systems upload data to centralized databases, providing near real-time access to data and the ability to monitor patient safety and compliance with the treatment and protocol. With each improvement in data quality and the ability to monitor data in near real-time, eCOA

**Table 2.** Forms of COA

| COA TYPE | RATER | COLLECTION METHOD AND CHARACTERISTICS |
|---|---|---|
| Patient-reported outcome (PRO) | Patient | Directly from the patient without amendment or interpretation by anyone else |
| Clinician-reported outcome (ClinRO) | Clinician | By trained healthcare professional (HCP) after observation of signs, behaviors or other physical manifestations in patient |
| Observer-reported outcome (ObsRO) | Observer (such as parent or other caregiver) | By someone other than the patient or HCP after observation of signs, behaviors or other physical manifestations in patient |
| Performance outcome (PerfO) | Clinician or Nurse | Based on task performed by the patient according to HCP-provided instructions to assess motor (e.g., 6MWT), sensory (e.g., visual acuity, Romberg's test) or cognitive (e.g., memory recall) status |

**Figure 1.** Alarms in eCOA studies improve data collection completion




systems support risk mitigation strategies in rare disease trials and deliver reliable, valid data—both of which reduce the time needed for database lock, keeping studies on time and on budget.

Moreover, data collected through eCOA are accepted by regulatory bodies. Data meet the ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) standard in the FDA Guidance for Industry Computerized Systems Used in Clinical Investigations[4] and the EMA reflection paper on the expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, which not only include ALCOA, but expand on it to include the attributes of: Complete, Consistent, Enduring, and Available when needed.[2]

> **Training caregivers on how to report on an ObsRO is a critical element to the success of data capture in rare disease studies.**

## Ensuring Consistent Data Collection

Uniform administration of assessments in clinical trials is required to reduce rater variability and minimize data risk with COA implementations. Furthermore, effective assessment training remains a key determinant of whether a therapy attains efficacy and/or safety. In fact, the FDA, EMA, and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommend that clinician raters, patients, and caregivers capturing assessment data receive training in the correct use of the instrument and of the electronic data capture element.

Training site raters and subject/caregivers is vitally important in rare disease studies, because inter-rater variability is high due to the widespread geographic dispersion of sites and subjects. In addition, rare disease research often requires event and severity reporting by caregivers, who do not inherently understand how to complete assessments. The role of

an observer—a neutral reporter, who reports only on what they actually observe—is very different from the role of a caregiver. Caregivers can spend in excess of 40 hours/week providing care and have substantial physical and emotional tolls that often cause their stress level to be 20-30% higher than the patients in their care. Training caregivers on how to report on an ObsRO is a critical element to the success of data capture in rare disease studies.

Training subjects and caregivers also promotes compliance. More than 75% of patients report that the number one factor that would motivate them to complete a daily diary in a clinical trial is training on the importance of their role, what to expect in the study, and the purpose and importance of the questionnaires.[5] The FDA PRO Guidance cites training of site raters, patients, and caregivers as the leading factor that is imperative to collecting the highest possible quality data in a clinical trial and the further complications that occur in rare disease essentially necessitate such a course of action.[6]

## Conclusion

Successfully developing new rare disease treatments doesn't have to be rare. Clinical trial sponsors who incorporate effective data capture strategies to optimize outcome measurement reduce clinical data risks, improve data quality, and strengthen their risk management initiatives through near real-time data access, all of which produces a more accurate picture of treatment benefit and keeps development plans on track and on budget. Utilizing electronic data capture systems and training site raters, subjects, and caregivers are important tools to ensure high quality data capture.

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# Empowering CRAs in Rare Disease Studies

Paul Bishop, Lyle Camblos

## CRAs have a wealth of skills and expertise to apply to high-touch, complex rare disease trials

Rare disease clinical trials require extraordinary customer service in many areas, even package delivery. In one case, each treatment dose cost more than $3,500, required constant refrigeration within a narrow temperature range, and had to be checked in and out to document protocol compliance and chain of custody. Often, the task fell to the trial's clinical research associates (CRAs), who went well beyond their job description to ensure the trial succeeded.[1]

Clinical trial performance can be improved by empowering frontline employees—most especially CRAs. Since CRAs spend the most time with study site staff and patients' charts, they are a rich source of detailed, real-world knowledge needed to identify and solve unanticipated problems. While valuable in any trial, harnessing these insights is especially important in the growing rare diseases segment, where small populations often mean trial designs must be tweaked mid-study, and retaining all the patients can be critical for trial success.[2]

Too often, however, valuable CRA resources are lost. The worldwide CRA turnover rate remained above 25% through 2015, and lack of internal career development opportunities was a significant factor, according to a long-running annual survey.[3] Such high CRA attrition often undermines continuity, which is imperative to the success of complex clinical trials.[4]

Because rare diseases affect so few people—defined in the U.S. as less than 200,000 individuals or about 6.3 per 10,000; less than five in 10,000 in the EU; and less than four in 10,000 in Japan—study populations are also small. In 2013, the average number of patients enrolled in Phase III clinical trials was 731 for orphan drugs, or about one-fifth the 3,540 for non-orphan drugs.5 However, these averages don't capture how truly small many orphan drug trials actually are.

For example, a 2009 study of 32 successful orphan drug pivotal trials for neurological indications identified 10 with 50 or fewer participants—including four enrolling just seven, 10, 17, and 18 patients.[6] Similarly, a 2014 study of 24,088 interventional clinical trials of all stages found that 72% of orphan trials enrolled 50 or fewer patients compared with 43% of non-orphan trials.[7]

Clearly, rare disease is a market segment sponsors cannot afford to ignore. More importantly, rare diseases require a different approach to clinical trials, as well as highly motivated and skilled CRAs to carry it out.

### The case for highly-skilled CRAs

Small study populations present unique challenges that may include:[2,8]

- Incompletely understood disease pathophysiology
- Unknown phenotypic and/or genomic variability
- Inconsistent or lack of a standard of care
- Thinly dispersed patient population
- Inexperienced research sites

As a result, the standard approaches to executing

a clinical study that may work for well understood, more common conditions with large patient populations are less likely to succeed for rare diseases. Due to the complexities rare disease trials present, it is crucial that the trial's frontline managers—CRAs—play a more creative, proactive role.

Often, rare disease trials are a journey of discovery—not just about the treatment, but also about the disease for clinicians and researchers alike. Close coordination among research sites and central trial monitors, including uniformly introducing protocol changes, such as dosing or outcome measure adjustments, is essential. As the primary liaison to research sites, CRAs are responsible not only for implementing any changes, but also for monitoring their effectiveness and collaborating on further changes as active members of a quality improvement team.

The importance of flexibility is illustrated by a study of a rare eye disease, in which blinding fibrous membranes grow under children's eye lids. The initial protocol called for clinicians to visually estimate lesions size, but this produced inconsistent data from visit to visit. Observers troubleshooting in the clinic saw the problem was squirming children. A solution was devised: substituting a central scorer to grade lesions using electronic analysis of digital photographs. This ensured the trial's success.[7]

Site and patient recruiting also may be very different for rare disease trials. For example, the usual large trial model of selecting experienced research sites and waiting for patients to accrue may need to be reversed. With patients widely and remotely spread, it can make more sense to find them first, and then work with an accessible clinic to set up a research site. Close support from onsite CRAs is required to bring up and support inexperienced sites.

In addition, CRAs may need to address patient needs, from clinical issues to arranging transportation and housing for patients who must travel, and even help manage their schedules to ensure they can stay on protocol. For example, in a trial of a drug for hereditary angioedema, CRAs supported sites by flying across the U.S. immediately when any patient had acute attack and needed to then rapidly enroll in the trial. Moreover, they had to closely monitor infusion supplies, providing a range of needle sizes to ensure that smaller veins could be used for patients undergoing dozens of infusions over the course of the trial. This same trial nearly failed early due to high turnover among CRAs provided by a large clinical research organization, and was salvaged when a smaller organization took over and assembled a motivated CRA team.[1]

## Cultivating a "founder's mentality" in CRAs

For success in rare disease trials, the range and technical complexity of the services CRAs must deliver, and the interpersonal skills needed to deliver them effectively, require that CRAs be highly trained, experienced, and motivated. Their ability to assess site performance and needs, and willingness to act independently to address them are especially important for supporting sites with limited clinical trial experience. The value of trained, competent, committed, and team-oriented CRAs can hardly be overstated.

Empowerment of frontline employees to improve organizational performance is hardly a new idea. Indeed, top management support for doing whatever it takes to improve quality and service is a central tenet of quality improvement theory as formulated and applied by W Edwards Deming and others to rebuild Japan's devastated industrial base into a world leader following World War II.[9] More recently, consultants Bain & Company have characterized it as harnessing the "founder's mentality," which includes:[10]

- A sense of mission to change the status quo on behalf of customers
- An obsession with the front line, characterized by an intellectual curiosity about every detail of the customer experience and of how everything in the business works, with decisions driven by instincts formed at the ground level, and empowerment of frontline employees
- An owner's mindset, characterized by a powerful sense of responsibility for employees, customers, products and decisions; an antipathy to bureaucracy; and a bias toward speed in decisions and actions

Bain's analysis found that as companies grow, many end up losing this "founder's mentality." This process starts in well-intentioned attempts to scale success, such as when an organization's original entrepreneurial heroes are asked to codify their success in SOPs, and professional managers are hired to enforce them. This leads to meetings at which no one at the conference table has contact with customers, and decision-making becomes increasingly less agile and customer-friendly. As this bureaucracy emerges, the talent attracted to the company is less interested in an insurgent mission, and more interested in the stability offered by carrying out a prescribed role in an established organization. In this way, growth can unwittingly dilute a firm's original edge, breed complacency, and generate an environment that no longer values the entrepreneurial problem solving that once made the company great.

The lesson for all organizations involved in clinical trials—whether sponsors or CROs—is quite simple: The role of the CRA is pivotal to corporate success. Specifically, empowering CRAs and instilling in them an owner's mindset could improve corporate performance.

Interestingly, our changing technological landscape could end up playing a major role in the continuing evolution of the CRA as a key player in clinical trial development. According to a recent survey of industry research experts, sponsored by

SCORR Marketing and A*pplied Clinical Trials*, the role of the CRA has changed more than any other job over the past 10 years, and will likely change the most over the next five. Increased availability of technology, including EMRs and RBM, were seen as the most important change drivers.[11]

These changes may bode well for better engaging CRAs in improving clinical trial performance. In particular, risk-based management, which shifts CRAs' focus from mechanically reviewing 100% of source documents to a more proactive troubleshooting and advisory capacity for sites, will help make better use of the high skills most CRAs bring to their jobs.[6]

As we alluded to throughout this piece, CRA engagement is essential to the success of rare disease trials. Maybe it is a judgment call to extend a visit by a day to provide extra training to site nurses on a new procedure. Maybe it is buying a site a better stethoscope for cardiac monitoring when inaccurate readings impede patient screening. Such solutions are born of a trusting, face-to-face working relationship, which may be difficult to develop from a remote call center. Recruiting CRAs with exceptional experience and commitment to customer service is a big factor, candidates who internalize the "founder's mentality" if you will. And adopting a CRA-first culture can pay off—doing so has driven our turnover rate to between one to four percent annually for the last 10 years.[8]

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