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APPLIED CLINICAL TRIALS

Going the Distance:
Insights into Rare Disease Clinical Studies, Trial Retention & Patient Experience

- Challenges & Opportunities in Clinical Research
- Orphan Drug Development Challenges
- Travel Services and Patient Retention
- Evidence Challenges and Solutions

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Understanding Rare Disease: Challenges & Opportunities in Today's Clinical Research

From patient retention to regulatory and ethical complexities, clinical research takes on a unique and challenging form in the realm of rare disease. Join us as we explore the profound impact of patient experience and the pivotal role of patient advocacy groups in achieving clinical breakthroughs with KimberLee Heidmann, Executive Vice President of Patient Experience and Customer Success at Scout Clinical.

Q: What defines a rare disease? What makes clinical research in this area unique compared to more common diseases?

KimberLee Heidmann: In the US, a disease is considered rare if it affects fewer than 200,000 Americans. Other countries will have slightly varying parameters for what's considered rare. There are somewhere between 7,000 and 10,000 identified rare diseases.

From a clinical research perspective, the most important factor is finding the patients. One of the biggest issues for rare disease families is getting a diagnosis. A lot of times people will have symptoms, or parents and caregivers will see symptoms in pediatric rare diseases, but their general doctor may not understand. The doctor may see symptoms that point to a specific rare disease that they've heard of, but a general practitioner or pediatrician might say it's out of their realm, or that it's some other disease or disorder or viral infection. Patients need an appropriate diagnosis, and then they need to be treated or have access to a physician that actually knows what research is available.

Another unique element is that there actually isn't much research out there. Not many companies are researching treatment for rare diseases, and somewhere between 90 to 95% of rare diseases have no available treatment. If there are at least 7,000 known rare diseases, and 90-95% have no treatment at all and are mostly treated off-label, just doing the math on that tells you how much research needs to be done.

Q: How does the rarity of a disease impact the recruitment and enrollment of participants for clinical trials? What are the specific challenges?

KimberLee Heidmann: First, you need a sponsor willing to do the research to find treatment. In some of these rare disease cases, there is no curative therapy. There are some rare diseases where the disease progression and the etiology of the disease is not as well known, so a lot of the research that we're doing is on disease progression rates. The drugs or the treatment that may be already available are designed to slow progression. Patients aren't going to take this drug and be cured of their disease.

For many families pursuing care where there isn't a cure, they're looking to extend the life and the quality of life for their loved one. Or in some cases, adult participation in clinical research may help extend or increase the quality of their own life, but in a lot of ways, participating in that research is altruistic because it's planning for the future. It's thinking about the impact of that research on future patients and for our loved ones and descendants down the line. So, you've got patients and families that enroll in clinical research because it

gives them hope for the future. If there is no other treatment or curative therapy, research may provide an extension of the life that they have with their loved one and the quality of that life.

But specifically, and logistically, it's very difficult. Once rare disease patients receive a correct diagnosis, and those patients are qualified for an active study, then they need to locate and travel to where that research is being conducted. A hot topic in research right now is cross-border enrollment in global clinical trials. With the emphasis on increasing diversity in clinical research, we're trying to find patients all over the world of different socioeconomic representation, or genders and ethnicities, or patients who live in cities versus rural areas, and so on. These factors impact their participation in the trial as well as outcomes. Once you've found those patients and identified where they can be treated, how can you get them to the site for treatment? It's a two-fold challenge.

Q: Speaking of cross-border enrollment, how does the regulatory landscape surrounding rare disease clinical research impact trial logistics?

KimberLee Heidmann: The cross-border enrollment piece has really impacted regulatory complexity. Let's say there's a trial in a disease that specifically affects people in a certain part of the world. While patients may be affected by the disease in one region, there may be no treatment centers in their home country. How do you get patients involved when they're not actually going to be engaged in the study until they reach the site?

The discussion around how to get consent from the patients, make sure that they're receiving treatment at the facility that can be covered under the clinical research piece of the study, and that they're getting standard of care through their physician at home presents a very unique set of challenges. Another major component we're dealing with is data privacy, which is a general global concern, but especially so when it comes to clinical research. Participant privacy is so important—not just for their personally identifiable information, but their protected health information as well. We must design the consents correctly for this unique model, put the right language in the form in a digestible way, and get approval from the IRBs and ECs.

There are a lot of complexities around this that you wouldn't see in a trial where the patient is being consented at a site local to their home, perhaps even in the same hospital with their primary care physician. If I'm moving a patient from Egypt to Turkey to participate in a clinical trial, how am I presenting that data compliance in the ICF so that it can be approved? Or how are we approaching that while the patient is consenting to share their data with Scout Clinical, they're not necessarily consenting to participate in the trial? There are significant regulatory considerations that must be made.

Q: In addition to data privacy and consent considerations, how can researchers ensure the ethical conduct of clinical trials for rare diseases?

KimberLee Heidmann: Data privacy and informed consent are step one. We have to present the information in a way that is understandable to the patient. They have to know all the potential benefits and risks. They also need clarity around reimbursement for out-of-pocket expenses, stipends, or time and wage loss compensation. Those types of things have to be very clearly outlined.

Step two, when you talk about ethical conduct with rare disease, there is often a more significant burden on the patient and the family to complete study visits. For example, let's say you have a pediatric patient with DIPG (diffuse intrinsic pontine glioma), a highly aggressive and hard-to-treat brain tumor. Very specific hospitals are treating and researching this, so the patient is potentially going to be traveling long distances for treatment. DIPG patients are severely compromised in terms of needing special equipment just to be able to sustain the travel to the visit. We have to think in terms of an ethical perspective; we have to think in terms of patient need. We must look at the burden on the patient and their care circle to establish what we can do to offset that burden.

In clinical research, the potential for patient services like travel support and reimbursement to be perceived as coercion is serious. In the rare disease space, this should be a very different conversation from a regulatory perspective, because the burden on these patients to actually complete their visits is different from the burden of many other therapeutic areas. In most cases these patients will require more extensive travel support (or Patient Navigator support where they're receiving white-glove, customized service) or more offset of financial burden just by the nature of their disease process and the location of the clinical research facility.

Q: What role do patient advocacy groups and foundations play in advancing rare disease clinical research? How can researchers effectively collaborate with them?

KimberLee Heidmann: In my opinion, the most important role that they play is giving a platform for the patient voice and keeping families from feeling isolated. Rare disease families can feel like they've been abandoned by the healthcare system. They may have been telling their providers about their child's or their own symptoms and were told that it wasn't a significant concern—or that it was some other illness, and it's not. When they finally receive an accurate diagnosis, they need support from others who have had a similar experience. Advocacy groups provide a space to be with other people who have had like experiences.

Once you get those people together and you give them a megaphone via an organized advocacy group, they can start to push that voice out to those who will listen. Advocacy groups have made a huge impact on sponsors:

listening to what patients need and putting the emphasis on research for these diseases and underserved populations. So firstly, they give the patients and their families a voice and secondly, they push research forward. They're the squeaky wheel saying, "We're finding new information about the disease, we want to know more about how we can help our families, and we want to know more about what our treatment can look like."

They also provide a wealth of information. For Scout Clinical, the advocacy groups are informing our services by telling us what patients and families need, which is going to positively impact our patients and therefore our sponsors because we're going to be able to retain those patients in a trial. We need to do everything we can to make their participation efficient and support them in that. Then we get the data, we get the outcomes, and we positively impact therapy in the future. Sponsors are able to bring the new drugs and new therapy to market, impacting future generations. It all works together, and it starts with the advocacy groups and the megaphone they give to the patient voice.

Q: What effect does the patient experience have on trial success? How can clinical trials be designed to optimize the patient experience?
KimberLee Heidmann: We need to change our perspective on how we look at the patient and the family or care circle experience in clinical research. In the past, people have had a bad taste in their mouth about research because of the use of the word "subject" or the traditional perspective that as a participant you're a "lab rat." The whole research industry has changed. We're starting to view clinical research as healthcare in light of underserved populations that are either uninsured, or underinsured, or don't have access to medical care.

Beyond changing that perception, we also must start looking at the patient and their family and what their experience looks like from a more humanized perspective. Clinical research participants are human beings; they are people of different ages, races, genders, and experiences. When we look at the patient as a whole person, we understand that their experience inside the trial will impact outcomes.

As employers and business owners, we treat our employees with a great deal of respect: we give them the desks, tools, and technology that they need. We need to do the same for these families and patients who are dedicating hours of their lives to working towards trial success. If they are supported in overcoming the barriers to their participation, that will optimize their experience–which ultimately affects the impact and the outcome of the trial.

Q: In your experience, what are some breakthroughs that have been achieved in the field of rare disease clinical research?

KimberLee Heidmann: We started Scout Clinical in 2016. Even though at that point I had been in the life sciences space almost 20 years, I don't think I understood the degree of influence to which the patient voice and interaction with participants and advocacy groups could potentially have on the clinical research industry. Since then, I've personally had the honor to watch the industry evolve and witness the conversation that thought leaders in our space are having about trial design, about how we view the participants in the trial and how we care for them.

Even since 2016, the transition to partnership and recognition of the role participants and their families play in clinical research has made giant leaps forward, specifically around rare disease and recognizing the patient perspective and feedback in trial design and available support services. There are so many technology providers, and service providers like Scout that have risen to the top to make changes in how we conduct clinical research. I think we should all be very proud of the breakthroughs but also keep going, because we still have a very long road ahead. I love the discourse that we're having, and everybody's getting involved in the conversation: big pharma, biotech, the FDA. The breakthroughs are significant, and it's very exciting.

ABOUT KIMBERLEE HEIDMANN

Scout Clinical co-founder KimberLee Heidmann has been part of the Meeting Protocol Worldwide family of companies since 2001. She now serves as Executive Vice President of Patient Experience and Customer Success, as well as the Global Head of Quality and Regulatory Affairs. Her career in life sciences began in 1998 at a subsidiary of the World Health Organization Mental and Behavioral Disorders Team. KimberLee was part of the core team of innovators responsible for bringing Atlas Clinical Academy to market in 2018. Her passion lies in driving transformative change in the clinical research field, creating inclusive pathways to research care for patients regardless of factors such as location, economic status, age, disability, or race.

ABOUT SCOUT CLINICAL

Scout Clinical, a member of the Meeting Protocol Worldwide family, offers a comprehensive set of services in travel, expense reimbursement, and payment management to ease site burden and help patients participate in clinical trials. Leveraging 25 years of life sciences industry experience and collaboration with leading pharmaceutical, biotechnology, medical device and CRO companies, Scout's clinical trial involvement spans from early and late phase to real-world research. Scout ensures patient stipends, lodging, and travel are seamless anywhere in the world and has successfully moved people and managed payments in over 100 countries for nearly 1,000 studies.

Whether a study involves 2 patients or 20,000, Scout tailors each experience to sponsors' unique needs and regulatory requirements: country by country, site by site, visit by visit. With the motto "No request is too large or too small," Scout Clinical is dedicated to helping patients stick with it.

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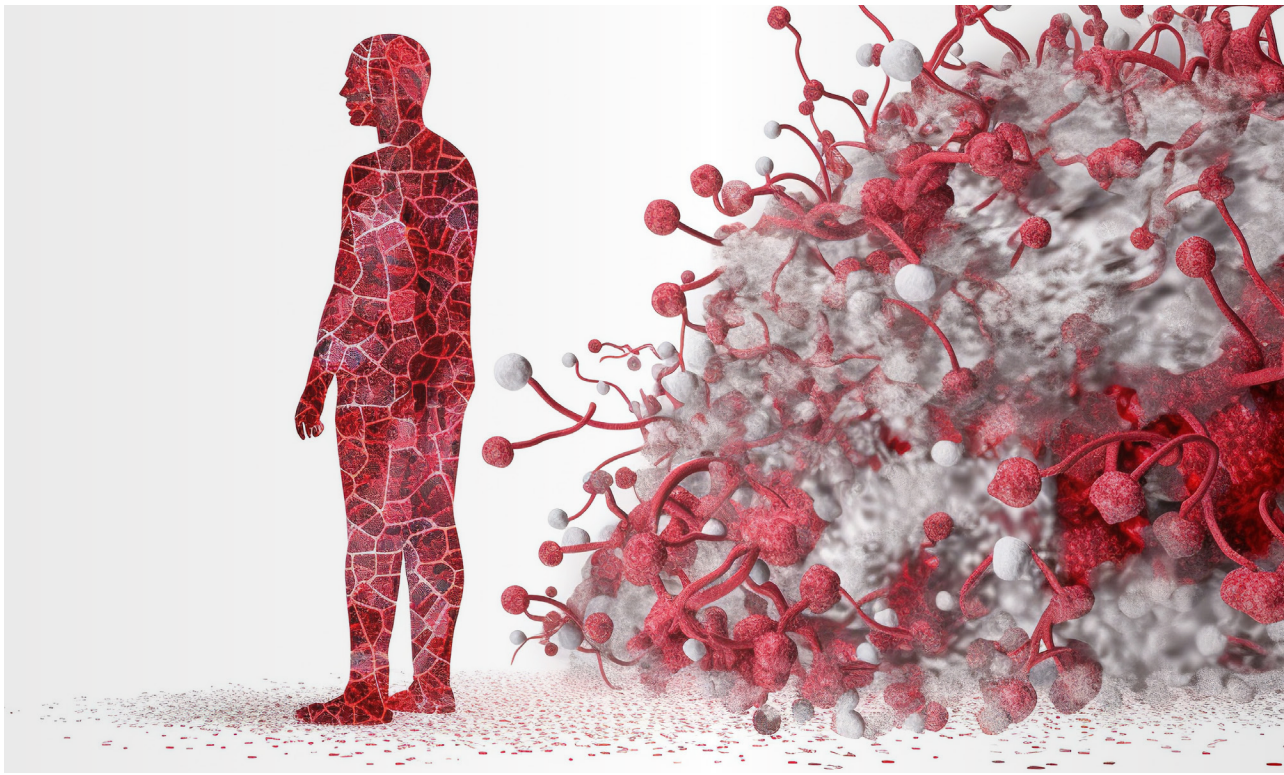

Rare Diseases: Meeting the Unique Challenges of Orphan Drug Development

By Michael F. Murphy, M.D., Ph.D.

Poor understanding of the natural history of the proposed indication due to few observational studies studying disease progression, heterogeneous patient populations with variable phenotypes and clinical courses, geographic dispersion of patients and investigators, regulatory uncertainties, and lack of prior clinical studies to establish a template for study execution can all prove challenging in creating a pharmaceutical development program for the treatment of a rare disease.

While individually rare, orphan diseases are actually collectively common, with an estimated 350 million sufferers worldwide. Since the introduction of the US Orphan Drug Act more than 30 years ago, the number of orphan designations has skyrocketed and experts are predicting worldwide sales of these drugs will reach $176 billion by the end of 2020[1]. With the cost of developing orphan drugs comparatively less than non-orphan products, appreciable regulatory support for innovative program design, and with the possibility of demonstrating significant intellectual property value, interest and investment in orphan disease development programs has been explosive.

Creating a pharmaceutical development program for the treatment of a rare disease can, however, prove to be a monumental task. Poor understanding of the natural history of the proposed indication due to few observational studies studying disease progression, heterogeneous patient populations with variable phenotypes and clinical courses, geographic dispersion of patients and investigators, regulatory uncertainties, and lack of prior clinical studies to establish a template for study execution, can all prove challenging. In addition, small patient populations isolated in a few tertiary care centers go against traditional methods of study operation. With at least 7,000 rare diseases, each exhibiting diverse symptomatology, the key differentiator for CRO engagement frequently is expertise in problem solving, and passion for clinical development rather than disease-specific experience.

THE IMPORTANCE OF THE PATIENT

In an orphan drug trial, clinical management of individual patients can be difficult. Understanding the burden of disease and managing patient and family experience within a study is key. Patients with a rare disease frequently arrive at a diagnosis through a lengthy process of evaluations and may be experiencing a reduced quality of life and, in some cases, limited life expectancy. In rare disease trials, the need to recruit and retain patients while adhering to exceptional standards of care influences every decision. The protocol must account for the vulnerability of the patient population and address ethical considerations, particularly if the study design mandates discontinuation of ongoing therapy considered essential for patient support. Eligibility criteria always influence the number of available subjects, and if artificially constrained, reduce the likelihood of establishing a clinical trials database from which evidence of efficacy and safety can be extrapolated to a larger network of representative patients with the same disorder.

It is well-documented that rare diseases exert a substantial physical, emotional, and financial impact on patients and loved ones. Many rare diseases are fatal in infancy or childhood. Children who do survive to adulthood face difficulties transitioning from pediatric to adolescent to adult care,

and frequently the clinical presentation will evolve. Furthermore, treatment often involves multiple specialties such as neurology, gastroenterology, psychiatry, endocrinology, cardiology and physical therapy because clinically important comorbidities are common. Assuring care coordination in the context of an interventional study is important. CRO partners will be able to assist sponsors in considering all these factors when creating the study plan, obtaining input from key opinion leaders (KOLs) on diagnostics, outcome measures and care processes that can help inform trial design and study metrics.

Despite these challenging circumstances, patients with rare diseases and their caregivers are typically well-informed about their condition. Thanks to the wealth of information available via the internet and social media platforms, they have easy access to information regarding disease management and treatment options. They are also more engaged with not only their healthcare providers, but also with other patients with similar conditions, and use social media extensively as an exchange platform for emerging basic and clinical research data.

In order to enhance the clinical trial process for participants, as well as improve study outcomes, sponsors frequently utilize the experiences and knowledge of patients and caregivers in the process of trial design. By doing this, drug developers can gain valuable insight into experiences associated with a specific condition—after all, firsthand knowledge of what it is like to progress through site visits and procedures while managing an illness is not something that can come readily, or exclusively, from a professional point of view. This crucial input can then be used to develop 'patient-centric' trials that make participation as easy and informative as possible for the patient, while increasing efficiency and enhancing the sensitivity of study outcomes.

UNIQUE CHALLENGES

There are some fundamental differences between conducting trials for non-orphan drugs and those for orphan drugs, which present unique opportunities.

First, finding and activating feasible study sites and qualified investigators can be difficult. Selection involves identifying countries with a sufficient number of suitable study participants, then determining whether these patients are accessible, and finally, identifying centers of excellence with the therapeutic and operational capabilities to execute an observational or interventional trial requested. The nature of the indication emphasizes the importance of the medical, cultural and regulatory context as well as the standard of care and treatment pathways within each country of interest.

Smaller patient groups and, occasionally, a decreased likelihood of identifying and engaging patient advocacy groups, means identifying and locating participants can be extremely challenging, while retaining them for the full study duration is key particularly when modification in longer-term outcomes influence approval. If there is no patient advocacy group, general registries such as the Global Rare Disease Patient Registry and Data Repository[a], entities such as the National Organization for Rare Disorders and the European Organisation for Rare Diseases; as well as resources such as Orphanet[b] are invaluable as a first step in an algorithm leading to site identification and selection.

Once sites are selected, site-by-site recruitment, retention analysis and planning and specialized outreach, must be undertaken. When studying an orphan disease, every single patient's participation is vitally important given limitations in patient availability, and the exceptional impact the data from a limited number of patients may have on program development. Engaging sites, investigators, and patients to confirm acceptance of the study design is vital. Proactively engaging all stakeholders can foster a collaborative approach that facilitates recruitment, retention and commercial value long-term.

To ensure high levels of participant retention, sponsors must make the patient experience as smooth as possible and where practical, reduce the burden on the patient and caregiver regarding both visit frequency, and visit intensity (the number and complexity of assessments at a site). For example, in-home nurse visits cognizant of the need for GCP compliance could be offered when patient mobility is a problem, and financial and logistical assistance should be provided to aid any travel and lodging requirements.

PEDIATRIC RESEARCH

Approximately 50% of patients with rare diseases are children. Understandably, patient recruitment, retention and management can present more challenges with a younger demographic. Participants' physical, intellectual, and emotional growth, developing attitudes and beliefs, as well as family dynamics, all have an influence on their participation. It is key to strike a careful balance between reducing risk and discomfort, and obtaining meaningful data. To support engagement and compliance, sponsors frequently consider age-appropriate communication, particularly during the assent and/or consent process, and ensure that disruptions to family life and school activities are minimized.

Additionally, a pediatric rare disease study might only enroll one to three patients per year, per site and therefore, creative and proactive site management planning is vital for those professionals and other support staff who will have responsibility for patient management. Mutually beneficial relationships include the establishment of a proactive publication strategy, opportunities

for investigator sponsored investigations embedded into an overall program of clinical research, and assistance in the creation of physician and patient educational programs that would facilitate product adoption following approval.

AN EVOLVING REGULATORY CLIMATE

Although orphan drugs typically follow the same regulatory approval path as non-orphan products, securing approval for the trial designs often required in rare-disease studies can provide an exciting opportunity for innovation. The introduction of the Orphan Drug Act of 1982 has provided considerable impetus and subsequently, there has been a significant rise in the number of orphan drugs being successfully brought to market, using a mosaic of different program designs.[2] In fact, before the Act's introduction there were just 38 approved orphan drugs, compared with more than 460 today[3]. Acknowledging its success, Japan and the European Union have since mirrored the US' incentives and introduced comparable legislation, which offers tax credits, user fee waivers, and marketing exclusivity, to those developing drugs to treat rare diseases.

In August 2015, the FDA released an updated draft guidance which is intended to offer sponsors further support when tackling the common issues encountered in the development of orphan drugs[4]. While the issues addressed are also present in non-orphan drug development, the FDA highlights that many of the challenges are accentuated given the rarity of the disease and the gravity of the unmet clinical need, and therefore require special attention.

Interestingly, the guidance highlights the need for sponsors to gain greater biological, clinical, and epidemiological knowledge about the specific rare diseases under investigation, and suggests conducting natural history studies, through various forms of observational research in a companion development program. By conducting these studies that look at the progression of a disease from initial symptoms, formal diagnosis, through various clinical endpoints, the FDA suggests that companies will be able to design more efficient drug development programs. Additionally, as these studies also provide information regarding healthcare utilization in representative patients under standard of care settings, the data influence decisions for formulary placement and levels of reimbursements.

For sponsors, working with scientific and regulatory professionals who have experience interacting with authorities can offer significant benefits to advancing programs. For example, because of the breadth and depth of experience in other orphan indications, they can offer support in mitigating limitations that may be present in non-clinical data, provide a rationale for the use of non-validated biomarkers that nevertheless are "fit for purpose" in early phase investigations, as well as recommend innovative trial designs for proof of principle studies.

FINAL THOUGHT

All challenges considered, current market trends and industry predictions would suggest an increasing emphasis in considering unique genotypic and phenotypic information within a variety of larger indications under an umbrella of 'personalized medicine'. An interest in developing either repurposed or novel products for orphan indications represents a natural extension of this activity. As a result, the number of drugs that are successfully brought to market for a variety of orphan indications is likely to rise. However, securing regulatory approval for the trial designs required in this area requires an exploration of innovation in study design, appreciation of evolving regulatory guidance, and incorporation of patient and family perspectives into the scope and detail of the drug development process. Additionally, successful commercialization efforts are predicated on demonstration of value during the course of clinical development, requiring different types of trials capable of evaluating changes in overall healthcare utilization following the introduction of innovative therapy; i.e., an effort which evaluates the impact of novel therapy on a 'system of care' in order to enable patient access. Given the unique technology represented by these products, educational programs for physicians and patients enhance informed adoption.

By working with strategic partners who have the expertise and experience in designing and delivering these trials, and the passion to address unmet clinical needs, sponsors can implement effective patient-centric trials which will meet the special demands of this underserved clinical population.

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a. Launched in 2012 by US National Institutes of Health Office of Rare Diseases Research.

b Orphanet, led by a consortium of 40 countries, is a reference portal for information on rare diseases and orphan drugs, for all audiences.

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Specialized Travel Services Can Help with Patient Retention

By Franc Jeffrey

Clinical trials endure high drop out rates due in part to long schedules, high travel costs and long reimbursement times. Outsourcing specialized clinical trial traveling services can help alleviate this concern by allowing sponsors to efficiently manage travel and other expenses.

As many as 30% of subjects taking part in Phase III clinical studies drop out. Grueling schedules, high travel costs and long expense reimbursement times are all factors in these high drop-out rates, which can cause trial delays or even cancellations. It is crucial to keep subjects motivated and part of this can be achieved through efficient management of travel and other expenses.

Specialized clinical trials travel services have grown among the need to address the regulatory demands around subject confidentiality. A travel management company (TMC), as an independent organization, can navigate the regulatory pathways and access specific information on subjects, arrange reimbursement of travel costs as well as other expenses with the participants.

As an independent service, subjects are also given the choice as to whether to use the service. Those who did can contact the service provider directly. As the service is optional and is operated in conjunction with pre-approved travel and expense guidelines, Institutional Review Boards (IRBs) are satisfied that the subjects are not being enticed to use the service.

By assigning codes for the subject and the study in place of personal information, travel is organized on the subject's behalf. All the bills are sent directly to the TMC, where they are desensitized and then charged back to the sponsor. The sponsor's corporate credit cards cannot be used for any element of the travel reservation process, as the details of the subjects would appear on the credit card bills.

To guarantee that there is no leaking of personal information, the corporate accounts of the TMC are used for all billing, reimbursement and reservation processes. Using a three-stage manual check process, information is desensitized and then reported back to the sponsor, who are only able to see the subjects ID's, dates of booking, types of travel and cost (they are not able to access specific information on subjects). This level of reporting allows the sponsor to maintain control of costs and to ensure the subject IDs correspond with dates of clinic visits.

Expense reimbursement is a further aspect of the service which allows a TMC to pay subjects any out-of-pocket expenses or stipends directly to them. By using a TMC to handle such reimbursement, it means CROs don't have to deal with potential tax issues while managing expenses. For example, in Poland if you receive monies as a company or individual, it must be declared to the tax authorities even if it's a straight pass-through expense.

COMMUNICATION EQUALS CONFIDENCE

Specific agents are allocated to each study, allowing the subjects to become familiar and comfortable. Electronic profiles, which are in-line with data protection and also PCI compliant, are used to keep subject information up to date, and are used by agents to make reservations and expense reimbursements.

Proactivity is key when organizing travel arrangements for subjects. When the sponsor provides the study protocol to the TMC, it can determine the travel impact on the patient that the visits require. The TMC builds a travel schedule around the protocol science that can be communicated to patients when they are thinking of enrolling in the study. By doing this, the patient knows their time expectation, along with the "scientific" expectation. For example, a one-day visit to a clinic can be three days when travel time is factored in. In one study, when the patients leave the clinic, they are radioactive and therefore not allowed to fly. Their one-day visit is followed by four nights in a hotel before travel is permitted. In this case, the protocol

will say a one-day visit, but the real time involved is actually six—one night before, one day at the site and four recovery days.

A travel management service can be viewed by a study participant as a neutral party since they are invited to use the service and it is not required. This could allow them to communicate more to their agents to help them, which in turn can help build the participant's confidence. For example, air travel can be unnerving for subjects who require special care and assistance, such as those in wheelchairs or who require access to oxygen. By liaising with airlines and using established partnerships, a TMC can ensure travel is as seamless as possible for the subjects. If a subject requires specialized medical care while travelling, arrangements can be made for road or air ambulances, ensuring optimum comfort and medical care for the journey.

MULTI-SITE STUDIES

Conducting multi-site studies can often be a daunting task from both a logistical and budgetary viewpoint. This is particularly true in emerging markets, where there are often cultural differences and language barriers to overcome. By utilizing the services of a network of global partners, the TMC ensures the service providers can draw on valuable local knowledge, such as familiarity with travel requirements relevant to the customs unique to that region.

For example, during one trial, subjects from Paraguay were happy to travel by ferry from Montevideo to Buenos Aires and back again in one day, in order to receive infusions. In the same study in the United States, subjects arrived in the town where they were to receive their infusions the evening before, in order to arrive at the site first thing in the morning, they spent all day there before departing for home. In Russia, the same trial allowed subjects to relocate to the city of their trial site for the duration of the research, due to a lack of public transport infrastructure.

This level of knowledge, combined with a study timetable and details of site locations, allows for effective travel and expense budgeting for global and multi-site trials. Additionally, local currency expense reimbursements and all travel arrangements made using global partners are billed centrally; this offers research sponsors consolidated financial data from one reporting system and immediate visibility of study expenditure.

RARE DISEASE TRIALS

Subjects taking part in rare disease trials can often be travelling from many countries or indeed long distances within a country to just a handful of sites. Advance planning of

subject logistics is key to keeping control of costs. It is wrong to assume that travel between countries that are close in proximity will result in the best value for money.

The TMC can help with budgeting in these cases. Very often relocation can be a more cost-effective option than regular cross border travel. Relocation can also be less of an ordeal to the subject than a grueling travel schedule that can last a couple of years. A travel management service with clinical expertise will have the ability to help with relocation services.

A common error when planning trial logistics can be underestimating the size of a country. Certain studies, including rare disease studies, may only have three of four sites that are suitable for testing in any given region. It is easy to assume that domestic travel is relatively straightforward and cost effective, this is often not the case.

PRE-EMPTING PROBLEMS

The benefits of outsourcing these crucial aspects of clinical trials are numerous. Ultimately the sponsors retain control of costs and receive meaningful reporting. The CRO has a greatly reduced amount of administration, removing the hassle of organizing subjects travel and reimbursing expenses, allowing them to concentrate on their primary role.

Additionally, improved budget control and cost savings can help the sponsor reduce expenditure through providing a study schedule that ensures travel can be effectively planned in advance. In turn, this ensures smooth travel arrangements, which leads to improved continuity in studies, happier and motivated subjects and a reduced risk of missed appointment visits or subjects leaving a study early, which are both an inconvenience and an expense to the sponsor.

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Shining a Light on Rare Disease: Evidence Challenges and Solutions

By Catherine Tak Piech

Significant challenges still lie ahead, but several specialists and a plethora of new technologies are well positioned to gather and analyze the evidence needed for diagnosing and treating rare diseases.

The global rare disease community is steadily increasing awareness of the plight of those <1 in 2000 people who suffer with rare conditions, which often makes them the orphans of the health care system. Their most recent efforts have been focusing on the repercussions of a delayed or missed diagnosis, and the heavy social and financial burdens rare disease patients and their families share.

On Rare Disease Day, February 28th, campaigners nationwide mobilize events to literally shine a light on the challenges faced by this community. This includes illuminating buildings, monuments and homes with Rare Disease Day colors: blue, green, pink and purple. Participants also wear zebra stripes to signal the need for clinicians to consider a rare disease diagnosis sooner.

The numbers are there. An estimated 300 million patients worldwide have diagnoses related to 7,000 unique rare diseases. More than 70% of these diseases are genetic in origin. Now that scientific advances are increasingly making new treatments feasible, governments are taking a closer look at rare disease populations and the need for reallocating resources.

The U.S. Government Accountability Office (GAO) recently issued a 100+ page report[1] investigating rare disease prevalence and associated costs in the United States. However, the report indicates that a complete picture of costs is obscured by limited evidence.

EVIDENCE CHALLENGES: INCOMPLETE DIAGNOSIS AND COST DATA

The GAO highlighted multiple data gaps in the rare disease landscape. Enumerating patients is problematic for several reasons: lack of specific diagnostic tests, delayed diagnosis or missed diagnosis, lack of specific ICD-10 codes and treatment, and simply the rarity itself.

The true costs of care are difficult to track. This is because of these diagnostic difficulties AND because many non-medical and indirect costs are broadly distributed across patients, their families, and society. Meanwhile payors—both public and private—focus on the direct medical costs. According to "The National Economic Burden of Rare Disease Study Summary Report,"[2] non-medical and indirect costs (e.g., loss of income, special accommodations and travel to appointments) could account for more than half of the nearly $1 trillion annual cost of rare diseases in the U.S.

A full accounting of rare diseases and their costs is needed to fully appreciate the challenges these populations face, and secure the resources necessary to improve the lives of those affected. The more information we have, the better we will be able to understand the value of new treatments.

Scientific progress in rare disease etiology, which seeks to determine the origin of disease—as well as the rapidly evolving potential for gene and cell therapies to deliver treatments—is driving the need for better information. Employing epidemiologists, data scientists, health economists, new data collection technologies, global outreach, and new platforms that can synthesize data from a variety of sources can help meet this need.

SOLUTIONS

The good news is the specialized skills and approaches needed to develop a more complete picture of a rare disease

population—including costs of care, treatment effectiveness and value—are also evolving rapidly and being adopted by both big pharma and more agile data driven startups. Some examples include:

- Deploying artificial intelligence and machine learning to scour the ever-expanding volume of scientific literature with greater precision, which identifies more relevant published data for rare disease populations.
- Using RWD from insurance claims and electronic medical records (EMRs) to develop external, or synthetic, control arms.

This will give new treatment studies a valid comparator, given the small number of patients overall and their reluctance to participate in a trial that requires randomization for what is often a severe disease. Real World Datasets can also be used to estimate the incidence and prevalence numbers needed to support an orphan drug designation application, undertake a survival simulation, develop a budget impact model, model an innovative pricing approach, and more.

- Deploying natural language processing within EMRs to identify the "bag of words," or symptom constellations, that are associated with a rare disease.

Having the ability to work backwards from a verified diagnosis may provide the data needed to shorten the time frame for identifying a rare disease. Developers could embed an alert within an EMR to help providers link symptoms to a rare disease.

Leveraging global epidemiology knowledge and contacts to tap into more comprehensive electronic medical records in countries with centralized health care systems, such as Scandinavia or Israel, and utilizing the resources of the National Institutes of Health-supported "The Undiagnosed Diseases Program and Network"[3] initiative, and its global counterpart, "The Undiagnosed Diseases Network International".[4]

- Partnering with specialized dataset owners and rare disease advocacy groups who devote significant resources to counting their constituents.

Rare disease advocates have strong incentives to better understand their community, and may benefit from data linkages that cross medical, genetic, geographic, socioeconomic, behavioral, and employment spheres. Having a more complete picture of their disease produces a powerful narrative for support.

- Establishing data-sharing research relationships with rare disease centers of excellence or referral centers, many of which are university based.

Utilizing decentralized tools—including telehealth, wearables, sensors, visiting nurses, home lab tests, ePROs, data

collection portals, etc.—to collect more comprehensive, longitudinal data and make it easier for patients to report symptom frequencies, disease limitations, costs, and functional improvements. This will provide a more robust picture of the impact of new treatments.

New data visualization technologies, such as interactive dashboards developed by Genesis Research and other industry advancements, are providing the ability to analyze and then communicate data more effectively to researchers, regulators, providers, payors, patients, and their families.

CONCLUSION

There is a dire need for better information to support development of treatments that address the costly, unmet needs of rare disease sufferers. While the life sciences community still faces challenges acquiring data for diagnosing and costing, there are several specialists (including data scientists), and a plethora of new technologies that are well positioned to gather and analyze the evidence needed for diagnosing and treating rare diseases, which will lead to a brighter future for many.

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